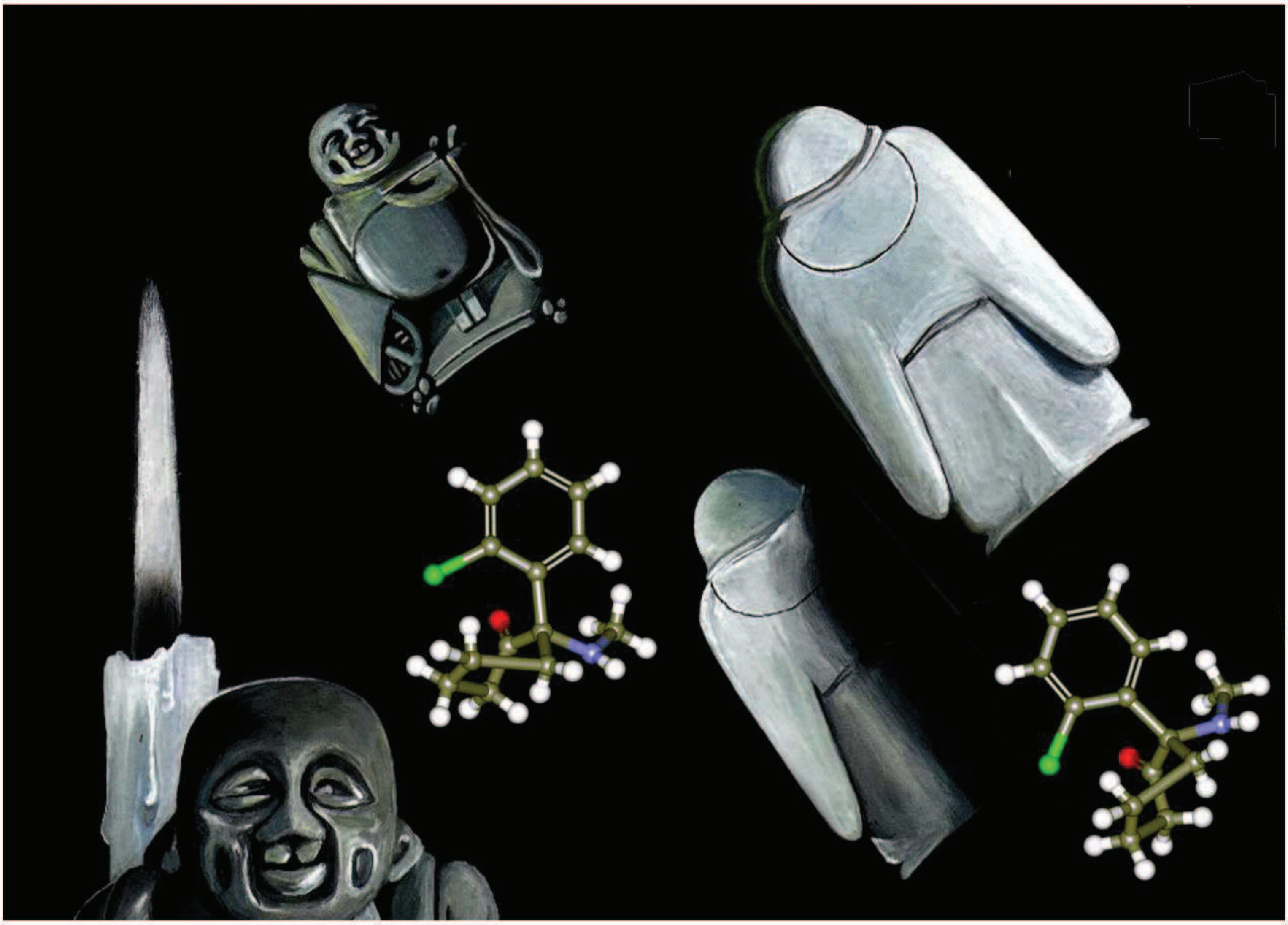
La lettre de Réanoxyo 12

VAL de GRACE : 7 Novembre 2002

Pathologies circonstancielles

Kétamine



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New clinical uses of ketamine in modern anaesthesia

in : "*Anestesia generale e speciale*", E. Romano (seconde édition, Trieste, 2002, à paraître).

Georges Mion[1], Jean-Claude Granry [2], Thierry Villevieille[1]
1-HIA Bégin, Saint-Mandé ; 2-CHU Angers

Ketamine's synthesis at the university of Michigan in 1965 participated in the myth of the creation of the « ideal » anaesthetic agent : cheap, no organotoxic effect, water-soluble, no irritations of the veins, no allergic reactions, broad therapeutic range with a very high margin of safety, free of important adverse circulatory or respiratory effects, administrations other than by the intravenous route, sedative, possessing hypnotic but also powerful analgesic properties (1). Commercialised as a racemate consisting of equal amounts of two optical enantiomers (Ketalar®), ketamine has been safely used in animals and humans for more than 35 years. Because of its analgesic and sympathomimetic properties, ketamine had been widely used for anesthesia in patients with shock, tamponade and asthmatic patients. Because it causes minimal respiratory depression and preserves spontaneous ventilation, it is particularly useful for short painful procedures in which relaxation is not required (i.e. reposition maneuvers, analgesia during delivery and diagnostic procedures). Because it is the only drug that can be administered by a route other than the intravenous one, ketamine is electively indicated for anaesthesia when a perfusion is not available, on the battle field for instance, or for intramuscular sedation or induction of anaesthesia with uncooperative patients, especially children. Because of all the above mentioned properties, ketamine has been largely used for anaesthesia for the burned patient.

Unfortunately, ketamine was progres-sively banished from usual practice because of the early noting of side-effects, namely psychedelic properties (word invented by an english psychiatrist, Umphrey Osmond, that means « mind revealing »). During the past 15 years, it has been supplanted by new, easier to handle drugs.

However, and in part because of the commercial availability of the new, short acting narcotic remifentanil (2) ketamine has been truly revisited (3,4,5,6). Indeed, the discovery of hyperalgesic states linked to the use of morphinomimetics prompted the search for a co-analgesic able to diminish this state and a renewed interest in N-methyl-D-aspartate (NMDA) receptor antagonists such as ketamine. Moreover, the noting of neuro-protective effects linked to the blockade of NMDA receptors led to a discussion of one of the major contra-indications of the molecule : brain-damage.

Opioid acute tolerance : Ketamine revisited

In the recent past years, it became evident that tolerance can develop rapidly from acute opioid exposure. The more the opioid administered, the greater the hyperalgesic effect. Both of these phenomena, tolerance and delayed hyperalgesia from opioid exposure, may reflect activation of NMDA receptors in the central nervous system (7). A series of studies suggest cross-talk between opioid receptor and NMDA receptors on the same cell. Phosphorylation of the NMDA receptor, secondary to activation of the opioid receptors, results in a release of the Mg^{2+} block, entry of Ca^{2+} into the cell, and activation of a series of intracellular cascades such as protein kinase C activation and prostaglandins and nitric oxide production that can lead to opioid receptor down-regulation (underlying tolerance) and hyper-responsiveness (underlying hyperalgesia).

Guignard et al recently demonstrated, in patients randomly assigned to receive either a remifentanil based anaesthesia or a volatile anaesthesia, that acute opioid tolerance develops in humans. Intraoperative hemodynamic response were similar in the two groups, but patients in the remifentanil group had greater postoperative pain scores and required nearly twice as much morphine in the first postoperative hours (8). Interestingly, Xiangqi et al demonstrated, in a rat model, that chronic administration of naloxone may prevent the hyperalgesia and allodynia that result from an incision (9).

With the new short-lived opioid remifentanil, one can now produce intense opioid receptor activation intraoperatively. However this has been recently put in doubt (10), rapid and extensive tolerance to this agent suggest this may not be good (2). Other potent opioids such as intravenous or intrathecal fentanyl, can actually induce a postoperative tolerance too (11,12). Cooper has suggested that epidural fentanyl may even induce a selective spinal hyperalgesia (13).

Ketamine, one of the two clinically available molecules blocking NMDA receptors (the other is dextrometorphan), but the only NMDA receptor antagonist currently approved for clinical use as an anaesthetic, has been experimentally shown to prevent opioid-induced hyperalgesia : systemically administered ketamine attenuates and reverses systemically induced morphine tolerance in mice and intraspinal ketamine attenuates tolerance produced by intraspinal morphine in rats (14,15). Célèrier et Al show that previous administration of ketamine prevents fentanyl-induced hyperalgesia in rats (16). Using cells which express both NMDA and mu opioid receptors, Gomes et al showed that the combination of morphine and ketamine resulted in a dramatic augmentation of phosphorylation mitogen activated protein kinase pathway, a marker of opioid receptor activation, which is enhanced by morphine but not ketamine alone (17). So, it became an interesting possibility, that ketamine could encounter a « second youth » through a use in combination with an opioid, in order to yield an opioid-sparing effect, and pain relief superior to either drug alone.

Analgesic properties of ketamine

The value of ketamine in the treatment of postoperative pain is a very controversial issue. Direct analgesic effect of ketamine and its effects on opioid-induced analgesia are not necessary related. But these two seemingly unrelated phenomena may have common neural substrates that interact at the level of excitatory amino acid receptor activation and related intracellular events. NMDA receptor is linked to pain processing and spinal neural plasticity. Peripheral tissue damage results in sensitization of dorsal horn neurons. One consequence is altered processing of afferent activity evoked by innocuous in addition to noxious stimuli, which is manifested clinically as allodynia and hyperalgesia. There is substantial evidence that the NMDA receptor plays a significant role in spinal hyper-sensitivity, triggering renewed interest in NMDA receptor antagonists such as ketamine as potential anti-hyperalgesic agents.

With a computer-assisted continuous infusion of ketamine, Bowdle et al showed that target plasma concentrations between 0 and 200 ng/mL (analgesic concentrations) produced dose-related psychedelic effects, similar to those found in a previous study with an illicit LSD-25-like drug. All participants had lateral gaze nystagmus at the 200 ng/mL target concentration. Several of them described altered physical sensations of body image : tingling sensations in the limbs, followed by numbness or floating sensations (18). Anaesthesiologists remain wary of ketamine adverse effects ; however, the distinction must be made between the use of high-dose ketamine as an anaesthetic agent (awakening from general anaesthesia in the range of 600-1100 ng/mL) and the use of low-dose ketamine for analgesic effects. In an outstanding study, Kissin et al demonstrated in 2000, in a rat model, that ketamine, in a dose not large enough to produce a direct antinociceptive effect, clearly decreased alfentanil-induced antinociceptive effect. Both alfentanil-induced adaptative changes - acute tolerance and rebound hyperalgesia - were attenuated by ketamine. The authors hypothesised that effects of ketamine related to nociception may be separated in three antinociceptive effects that require three concentrations of the drug. Effect on phasic pain occurs at subanesthetic doses (0.5 mg/kg), effect on tonic pain at subanalgesic doses (0.25 mg/kg) and attenuation of tolerance to the analgesic effect of opioids occurs at the smallest concentration (0.07-0.15 mg/kg), a third dose range in which ketamine has no analgesic potency on its own (19,20).

Ketamine acts on a variety of receptors including nicotinic, muscarinic, mu, delta and kappa opioid receptors, sodium and voltage-sensitive calcium channels. It particularly acts as a use-dependant non-competitive antagonist of the phencyclidine receptor site in the NMDA nociceptor complex channel. The rate of onset and recovery of the block depends on agonist binding at a different receptor site : the receptor channel has to be in the open state before ketamine can bind to or disassociate from the blocking site presumed to be situated within the channel pore. This raises the possibility that ketamine can become « trapped » in the receptor channel until the channel reopens after agonist activation. A second NMDA receptor binding site for ketamine has been reported that is associated with the hydrophobic domain of the protein. Binding at the former site (in the channel) increases channel open time, whereas binding at the lower site decreases the frequency of channel opening. The effects of ketamine on the NMDA receptor should not be considered « analgesic » but rather « anti-allodynic » and possibly « tolerance-protective » (19).

The mechanisms of antinociceptive and antihyperalgesic properties of ketamine may be different. In the absence of inflammatory reaction, systemic ketamine increases concentrations of noradrenaline and 5-hydroxytryptamine in the lumbar CSF. In rats, its antinociceptive effects are inhibited by intrathecal pretreatment with yohimbine and methysergide. On the other hand, intrathecal ketamine does not produce any antinociceptive effect, suggesting that ketamine activates monoaminergic descending inhibitory system at the supraspinal sites, but not at the spinal level (21). In a rat model of intraplantar carrageenan injection, Kawamata et al demonstrated that either intraperitoneal or intrathecal ketamine produces antihyperalgesic effects but with no involvement of the monoaminergic descending inhibitory system, suggesting a prominent role of NMDA-receptor antagonism with peripheral inflammation. Recent evidence has indicated that central sensitization of the wide dynamic range spinothalamic tract neurons attenuates the periaqueductal gray matter-evoked inhibition, indicating disinhibition. It could indicate that ketamine does not activate the supraspinal inhibitory systems because of disinhibition (21).

In man, ketamine has been shown to exhibit analgesic effects and to reduce hyperalgesia in a dose-dependent manner. Boluses of either ketamine 0.15 mg/kg or ketamine 0.30 mg/kg followed by continuous infusion of ketamine 0.15 mg kg/h or ketamine 0.30 mg kg/h respectively reduced the magnitude of both primary and secondary hyperalgesia in healthy volunteers in whom burn injuries had been produced with a thermode. Side effects were frequent but clinically acceptable (22). In a randomised, double-blinded, placebo-controlled study in volunteers in whom capsaicin had been injected intradermally, an i.v. bolus of 0.1 mg/kg ketamine followed by infusion of 7 µg/kg/min significantly reduced the area of hyperalgesia and it tended to reduce brush-evoked pain (23).

In a recent review, Schmidt et al reported the results of 28 prospective, randomised, double-blinded controlled studies with reported pain scores in man. Low-dose ketamine was defined as a bolus dose < 2 mg/kg when given I.M. or < 1 mg/kg when given i.v. or epidurally. For continuous i.v. administration, low-dose ketamine was defined as a posology of 20 µg/kg/min. There is no evidence that ketamine contributes to postoperative respiratory depression. Cardiovascular response to low-dose ketamine shows minimal changes in heart rate and blood pressure. Low-dose ketamine may cause mild sedation, but does not appear to aggravate opioid induced sedation. The incidence of nausea and vomiting (POVN) and of urinary retention is significantly reduced compared with morphine alone, maybe due to the opioid sparing effect of ketamine. Disturbing emergence reactions such as hallucinations and nightmares have limited the clinical usefulness of ketamine, but if the incidence varies from 5 to more than 30% after high-dose ketamine, this is not true with low-dose ketamine and in five out of six studies, results suggest that i.v. ketamine of less than 2,5 µg/kg/min does not cause hallucinations or cognitive impairment. Ketamine alone appears to provide satisfactory pain relief only at the upper end of the low-dose range with an increased risk of psychomimetic adverse effects. On its own, for certain clinical situations as asthma, ketamine might provide an alternative to conventional opioid therapy, but remains a rescue drug. As an adjunct with opioids or local anaesthetics, low-dose ketamine, especially in the « subpsycho-mimetic » range (blood concentration < 50 ng/mL) may play an important role in the management of postoperative pain. Either i.v. (continuous, PCA) or epidurally, ketamine reduces opioid consumption and prolongs and improves analgesia. The authors concluded that the concept of « balanced analgesia » merits attention given the limits of opioids analgesia (19).

In contrast, Ilkjaer et al were unable to demonstrate an additive analgesic or opioid sparing effect of ketamine 10 mg/h i.v. combined with efficient epidural bupivacaine and epidural morphine at 48 h after renal surgery. Patients who received ketamine felt significantly more sedated at 0-24 h, but not at 24-48 h after operation, compared with patients who received placebo. However, it is important to notice that in this study, visual analog scale (VAS) scores at rest were very low, because of efficient epidural blockade that may have prevented the NMDA receptor from being in the open state (24).

The analgesic effect of ketamine given as a continuous perfusion occurs at much lower plasma concentrations (100-150 ng/mL) than anaesthetic effect (700 ng/mL). At subanesthetic doses (0,15-0,25 mg/kg) which are about 10 times weaker than anaesthetic doses (2 mg/kg), analgesia is short lasting, about 30 minutes with an onset time of 30 s and a half-life distribution of only 10-15 min (25). For this reason it is certainly necessary to administer ketamine in a prolonged manner, in order to obtain a correct postoperative analgesia. This goal may be achieved either by continuous administration with an electric syringe (26), or administration directly in PCA. Results are controversial, but studies are few, and methodological problems may explain a part of the observed differences. Adriaenssens et al show, in 30 patients randomly allocated to receive a continuous infusion of 2.5 µg/kg/min ketamine or placebo associated with a PCA regimen of morphine, that cumulative and incremental morphine consumption was significantly lower in the ketamine group : 28 vs 54 mg for 48 hours. Nausea was less frequent in the ketamine group and no hallucinations were reported. Using a pharmacokinetic computer simulation (Stanpump®, Steven L Shafer, Stanford University), they calculated the infusion rate of ketamine set to produce a theoretical plasma concentration of 100 ng/mL to produce analgesia without important side effects. The initial rate of the ketamine infusion was 10 µg/kg/min, decreasing to 7.5, 5 and 2.5 µg/kg/min after 5 , 30 and 45 min respectively and was then maintained at 2.5 µg/kg/min for 48 hours. (26). On the contrary, Edwards et al found, in 1993, dreams to be a problem in a population of elderly subjects undergoing elective upper abdominal surgery who received ketamine 7.8 µg/kg/min in the postoperative period. Morphine consumption was not lowered in the ketamine group, but there were 4 groups of only 10 patients, and there were discrepancies in the groups composition (27).

Three other studies mention the use of ketamine directly added in the PCA regimen. Edwards et al showed in an in-house study, the compatibility of morphine plus ketamine in the same syringe (27) and Lau et al showed that a mixture of ketamine and morphine remains stable for 24 h at pH 5.9 raised with sodium bicarbonate in order to minimize local tissue irritation (28). Javery et al demonstrated that i.v. PCA ketamine 1 mg/mL in combination with morphine 1 mg/mL provides superior post-operative pain relief to morphine alone in patients undergoing elective microdiscectomy. The mean VAS pain ratting was lower for patients receiving ketamine (2.3 vs 4.5), with less side effects, reporting less nausea, pruritus and urinary retention. The incidence of dysphoria was low and not different in the two groups. The addition of ketamine had a clear sparing effect : the morphine group received almost twice as much opioid (51 vs 26 mg) during the first 24 hours (29).

On the contrary, in a double-blinded, randomised controlled trial involving seventy-one patients undergoing major abdominal surgery, Reeves et al concluded that small-dose PCA ketamine combined with morphine (1 mg/mL for both drugs) provides no benefit to patients. Postoperatively there were no differences between the groups for subjective assessment of analgesic efficacy, pain scores, opioid consumption, or adverse events. Morphine-ketamine patients performed worse in cognitive testing and had an increased risk of vivid dreaming (30). Recently, Kim showed in patients scheduled for total abdominal hysterectomy that ketamine 50 or 100 mg could be used in a PCA regimen with butorphanol 10 mg, ketorolac 240 mg and odansetron 4 mg for the postoperative period. Drug consumption was reduced by 28 and 38% in the ketamine 50 and 100 mg groups respectively. Sedation was higher in the last group, but the incidence of nausea and vomiting was diminished in the 2 ketamine groups (10%) when compared to control (40%) (31). Thus, the interest of adding ketamine in a PCA regimen still remains a debate, but further studies may clarify this exciting and promising research field.

Preemptive Analgesia with Ketamine

Repetitive C nociceptive-fiber afferent input results in an augmented response to subsequent C-fiber stimuli. This « wind-up » phenomenon is mediated by NMDA receptors and is due to a central temporal summation. As we saw earlier, nociceptive impulses may set off a prolonged and widespread increase in spinal cord excitability, underlying postoperative pain, and making very large doses of opioids necessary to suppress it. Moreover, one of the reasons for the failure to consistently observe a sustained effect of preemptive analgesia with large doses of opioids is perhaps an acute increase in dose requirement after such large doses because of acute development of tolerance, an effect that lasts for days thereafter (7).

Kissin defined preemptive analgesia as a procedure aimed to prevent the establishment of a central sensitization caused by incisional and inflammatory injuries, covering the period of surgery and the initial postoperative period. Ketamine inhibits central temporal summation in humans (32) and, in human studies comparing preincisional with postincisional treatment, most significant advantages were reported with ketamine (33). The goal of preemptive analgesia is to prevent or reduce the development of any « memory » of the pain stimulus in the nervous system. NMDA receptors seem to be receptors of « pain memory » and « wind up » is prevented by administration of NMDA antagonists which may reduce central sensitization (34). Guirimand et al showed in 2000 in a placebo-controlled study that the increases of the R_{III} nociceptive flexion reflex (i.e., wind-up) during high frequency stimulation is significantly reduced by small systemic doses of ketamine (0.15 mg/kg) (35).

Thus, ketamine may produce preemptive analgesia either by reducing « pain memory » in the spinal cord, or by lowering acute opioid tolerance. In a recent review, Kelly et al stated that the physiological basis of preemptive analgesia remain complex and that effective preemptive analgesic techniques require multi-modal interception of nociceptive input. Although the literature is controversial regarding the effectiveness of preemptive analgesia, it seems that regional anaesthesia, induced prior to surgical trauma and continued well into the postoperative period, is effective in reducing peripheral and central sensitization. Pharmacologic agents, especially when used in combination, act synergistically to decrease postoperative pain. Evidence points to non-steroidal anti-inflammatory drugs (NSAIDs), opioids, alpha-2-receptor antagonists and NMDA-receptors antagonists (36).

Indeed, Royblat et al showed in women undergoing elective open cholecystectomy that ketamine 0,15 mg/kg given intravenously prior to the incision reduced the need by 40% for postoperative PCA morphine (30 versus 50 mg for the first 24 hours) despite the fact that the pain scores were significantly lower in the ketamine group. Interestingly, mean blood pressure and heart rate were found to be significantly lower after induction of anaesthesia in the ketamine group (34). In contrast, Dahl et al failed to show any preemptive analgesic effects of a single dose of ketamine (0.4 mg/kg) given before abdominal hysterectomy procedures (37).

Local Effect

Recently, Wagner et al showed that ketamine interacts with sodium channels in a local anaesthetic-like fashion, including sharing a binding site with commonly used clinical local anaesthetics, an intrapore receptor (38). In a model of inflammatory pain induced by a burn in 15 volunteers, Pedersen et al found that ketamine (7.5 mg, subcutaneous infiltration), compared with placebo and systemic ketamine, had a brief local analgesic effect < 1 hr (39) . On the contrary, Gottrup et al found in a randomized, double-blinded, placebo-controlled study that local ketamine (5 mg) failed to change any measure in 12 volunteers with intradermally injected capsaisin, whereas lidocaine reduced all measures compared with placebo (40). In a randomized, double-blinded study, Lauretti et al demonstrated that Epidural S(+)-ketamine (0.1 and 0.2 mg/kg) resulted in prolonged analgesia in patients undergoing minor orthopedic surgery with combined spinal anesthesia (intrathecal bupivacaine 15 mg). The authors were not able to demonstrate any difference between the two doses and analgesia was enhanced by transdermal nitroglycerin, a NO donor (41). Miyamoto et al showed that intrathecal ketamine attenuated the development of morphine tolerance and increased the somatic (tail flick) and visceral (colorectal distension) antinociception of morphine in rats (42). De Kock et al recently demonstrated that sub-anaesthetic doses of i.v. ketamine (0.5 mg/kg bolus followed by 0.25 mg/kg/h) given during anaesthesia reduced wound hyperalgesia and proved to be superior to the epidural administration of ketamine in patients scheduled for rectal surgery under combined epidural/general anaesthesia. They hypothesised that the epidural block may have prevented the action of ketamine on spinal NMDA receptors because ketamine NMDA block is use-dependant. An epidural block which produces pre-synaptic inhibition of noxious afferents may have prevented the NMDA receptor from being in this open state (43). In its review, however, Schmidt states that there is little evidence that epidurally administered low-dose ketamine alone provides effective postoperative analgesia and that it is recommended that ketamine should not be injected intraspinally in humans (19). However, ketamine's neuronal toxicity is mainly caused by its preservatives. Hawksworth et al showed that intrathecal ketamine at doses higher than 0.7 mg/kg (0.7-0.95 mg/kg), produces both sensory and motor block in elderly patients scheduled for transurethral prostate surgery. The onset of motor block was within 2-3 minutes, peaked in 5-10 minutes, and lasted 30-60 minutes. Sensory block took 5-20 minutes to reach its maximal height. Maximum sensory block height varied from L1 to T7. However, despite adequate block to pinprick, half the patients sensed the diathermy and were given a general anesthetic, and the incidence of severe psychotomimetic side effects (30%) precludes ketamine use as a sole anaesthetic agent for spinal anaesthesia (44). The relative safety of spinal ketamine without preservative is not established, but evidence is accumulating that epidural ketamine (4-60 mg), although not a potent epidural analgesic alone, may have an additive effect with opioids or local anaesthetic drugs (45,46,47,48).

Chronic pain and cancer pain

Hyperactivity of NMDA receptors is an important factor in the genesis of neuropathic pain , where long-lasting changes in neuronal excitability and development of allodynia and hyperalgesia seem to be dependent on the activity of NMDA-activated synapses. It has been proven that excitatory amino acids (glutamate and aspartate) are responsible to sensitization phenomenon of central neurons, in particular, at the spinal level (49). Thus, ketamine may be a valuable alternative in a wide variety of chronic pain therapy, because NMDA-receptor inhibition by ketamine leads to a wind-down phenomenon, providing prolonged benefit. It reverses the right shift of the opioid response, which is typical of opioid-resistant pain syndromes, such as neuropathic pain, and this can be achieved with subanesthetic doses (50).

Besides improvement in the patients pain relief, ketamine becomes peculiarly valuable during the time-course of chronic pain, because of the possibility to use it by routes other than the intravenous one (51,52). Ketamine has a high parenteral bioavailability (93%) and low oral and rectal bioavailability (10-20%), both of which are subject to first pass metabolism and conversion to the active metabolite norketamine. Ketamine is metabolized extensively by the hepatic cytochrome P-450 system ; norketamine is only one-third to one-fifth as potent as the original compound but may be involved in the prolonged analgesic actions of ketamine (4,6). Intramuscular (IM) injection of ketamine at 0.5 mg/kg produces analgesia at the plasma concentration of 150 ng/mL. In a comparison study, the plasma concentration of ketamine (0.5 mg/kg) after 30 minutes was much lower in the oral group than the IM group, and yet the level of analgesia was comparable between the two groups. This may be due, in part, to the higher serum level of the metabolite norketamine (50,53). Indeed, the pain syndromes of three patients with difficult to treat, predominantly neuropathic pain syndromes were recently managed with the addition of low dose parenteral ketamine (40-60 mg over 24 hours) as an analgesic adjunct. The patients were converted to oral ketamine at doses 30 to 40% of the previous parenteral dose. Their pain syndromes remained successfully controlled on the lower dose of oral ketamine with remarkably few side effects (54).

Oral onset is delayed to 30 minutes compared to 15 minutes IM. Nasal ketamine has been used up to 6 mg/kg, but side effects of burning and bitter taste have been reported. Side effects caused by parenteral ketamine (dysperception, vivid dreams or nightmares, hallucinations and increased salivation) may be less with the oral route (53).

Chow et al demonstrated in 1998 that ketamine (10 mg bolus and 12 mg/h infusion) allowed a reduction of 40% of morphine / day in a patient who underwent four thoracotomies within a 3 month-period (55) and IM ketamine (35 mg) demonstrated benefits to a patient with chronic back pain after spinal surgery, associated the use of 1 g/day of morphine IM, in terms of reduction in morphine dose and reduction in pain scores with minimal side effects (56). Hoffmann et al reported the successful treatment of a case of intractable pain secondary to postherpetic ophthalmicus neuralgia in which stellate ganglion block, TENS, melitracen and flupentixol, mexiletine and clonidine, carbamazepin and morphine in association were ineffective. An IM bolus of ketamine 15 mg was proposed, followed by a subcutaneous infusion of 5 mg/hr (0.06 mg/kg/hr) given into the abdominal subcutaneous tissue (subq). Pain relief was obtained with only slight lightheadedness ; Within a week, other medication had been discontinued and the patient was able to ambulate without side effects. Oral ketamine was instituted and the effective dosage was 5 x 200 mg/day. The dose was then gradually decreased and eventually stopped without recurrence of pain (57). Eide et al report a similar efficiency of ketamine (0.15 mg/kg/hr subq via a portable infusion pump) in four out of five patients with post-herpetic neuralgia. Ketamine reduced the severity of continuous pain as well as the severity of attacks of spontaneous intermittent pain and allodynia. The most troublesome side effect was itching and painful indurations at the injection site which appeared after 2-3 days of drug infusion (58). Mion et al treated successfully with ketamine, (0,06 mg/kg i.v.) a neuropathic pain in a patient with traumatic spinal contusion. Pain completely disappeared after a few minutes and ceased for 5 hours without dysphoria. Relay was taken after 72 hours with 33 mg kétamine IM, but with mild dysphoria (59). Broadley et al reported two cases of chronic neuropathic pain unresponsive to a wide range of medications, whose treatment was effectively controlled with oral ketamine. A 31 year-old man with AIDS related neuropathy pain unresponsive to amitriptyline, carbamazepine, and morphine, was successfully treated with 200 mg/day oral ketamine with vivid but not unpleasant dreams as the only side effect. The pain of a man with syrinx in the thoracic cord with allodynia, was relieved with oral ketamine 100 mg qid for three months (53). Knox et al reported the successful treatment of a 17 year-old boy with an unbearable phantom limb pain, despite an association of morphine and carbamazepine and a sciatic nerve block. A kétamine infusion (10 mg/hr) allowed morphine to be completely stopped after 48 hours, with no evidence of hallucinations. After 4 days of continuous infusion, ketamine was administered with a PCA device to allow dosing flexibility : ketamine boluses of 3 mg with a lockout of 15 minutes were given with a background infusion of 6 mg/hr. With this regimen, the dose of ketamine averaged 9 mg/hr and the patient was weaned after a total of 14 days of ketamine with satisfactory results (60). Graven-Nielsen et al reported similar results in fibromyalgia patients (61).

In fact, Backonja et al showed in 1994, in a double-blinded placebo-controlled study that allodynia and hyperalgesia improved after the administration of ketamine (0,25 mg/kg i.v.) in a dose related fashion, in 5 out of 6 patients with chronic neuropathic pain (62). In contrast, Haines et al showed that oral ketamine gave rise to an extra-analgesic response in only three out of 21 patients with chronic neuropathic pain (14%). The authors found that adverse effects limited the use of ketamine in almost half of the patients (63).

Dramatic improvements have been observed especially in patients experiencing intractable cancer pain. One of the reasons why ketamine is so effective is perhaps because the NMDA block may be apparent only after the receptor channel has been opened by nociceptive stimulation (26,32). In the terminal stage of cancer, it may be very difficult to control the pain and one may end up having to perform neuroablative procedures. So cancer pain is a model of chronic and intense nociceptive stimulation.

Clack et al reported the case of a 39 year-old man with cancer of the maxillary sinus, with intractable pain, despite the use of transdermal fentanyl (1600 µg/hr), continuous iv (morphine 330 mg/hr) and intraspinal opioids. When the pain became unbearable, the anaesthesiologist was called and gave ketamine, 50 mg iv, which promptly relieved his pain for 30 minutes. An infusion was started at the rate of 100 mg/hr. During the following days, the epidural catheter and transdermal fentanyl were discontinued. Despite high ketamine doses, this patient never became anaesthetised (64). Mercadante and al observed synergism between ketamine and morphine in cancer pain patients who did not respond to high dose i.v. morphine. Single doses of 2.5 mg of IV ketamine resulted in dramatic improvement in previously uncontrolled pain in patients who then received continuous i.v. infusion of doses of 40-500 mg/day for a mean of 18 days. Excellent analgesia was reported even though daily morphine doses were halved (50). Subcutaneous continuous infusions of ketamine in doses of 60-700 mg/day is another way to achieve pain relief in cancer patients, with few side-effects (psychomimetic reactions, reactions at the injection site). One patient with extensive recurrence of a breast cancer, whose pain was not controlled with oral morphine 10 g/day was able to reduce the dose by 90% to 1g/day after the institution of subcutaneous continuous infusions of ketamine. Recently, ketamine has been used for more than a year by subcutaneous continuous infusion in a patient with neuropathic cancer pain, unresponsive both to oral and intrathecal morphine with bupivacaine. Ketamine was given in doses varying from 140-450 mg/day, while doses of morphine were reduced from 5g/day to 200 mg/day subq. The authors recommend a starting dose of 100 to 150 mg/day subq titrated to effect, and a halving of the daily dose of the opioid as initial therapy. Haloperidol 2-4 mg/day limits or even prevents psychomimetic side effects. On the basis of experience, ketamine seems compatible with haloperidol and morphine in the same syringe (50). Kannan et al stated that low dose oral ketamine is beneficial and effective in the management of intractable neuropathic pain in patients with advanced cancer but that its utility may be limited in some patients by the adverse effects that accompany its use. To evaluate the role of oral ketamine as an adjunct to oral morphine in cancer patients experiencing neuropathic pain, 9 cancer patients taking maximally tolerated doses of either morphine, amitriptyline, sodium valporate, or a combination of these drugs for intractable neuropathic pain, and reporting a pain score of > 6 on a 0-10 scale, were studied prospectively to evaluate analgesia and adverse effects. Ketamine in the dose of 0.5 mg/kg three times daily was added to the existing drug regimen. Seven patients exhibited a decrease of more than 3 from the baseline in the average pain score. Four patients experienced nausea, of which one had vomiting. Eight patients reported drowsiness during the first two weeks of therapy and this gradually improved over the next two weeks in 5 of these 8 patients. Three patients withdrew from the study, two owing to excessive sedation and another due to a "feeling of unreality." None of the patients reported visual or auditory hallucinations (65). Lauretti et al finally suggested that the World Health Organisation analgesic ladder could include new drugs to delay morphine tolerance and decrease the incidence of adverse effects related to high doses of opioids. They demonstrated in patients with cancer pain refractory to tramadol or NSAIDS and oral morphine 80-90 mg daily that 0.5 mg/kg oral ketamine every 12 hours diminishes morphine requirement with significantly less somnolence and apparently less constipation, nausea and vomiting (66).

Intrathecal administration of ketamine has been advocated as a compassionate protocol when cancer patients in end-stage disease experience unbearable pain. Muller et al described a case series analysis in which four patients, experiencing cancer pain with nociceptive and neuropathic components, were treated with a continuous intrathecal administration of ketamine (10 mg/day), because of intractable pain despite the use of an intrathecaly administered mixture of high dose morphine (20 mg/day in one patient), bupivacaine and clonidine. Patients were treated for 35 to 58 days, until their death, with a spectacular relief of their unbearable pain and without significant adverse side effects (67).

Ketamine and the brain : not contra-indicated any more

The use of ketamine in the presence of cranial trauma is still much debated because it induces cerebral vasodilation. Even recent reviews still affirm that ketamine is contra-indicated in patients who lack normal intracranial compliance (68). Ketamine is usually contra-indicated in neurosurgical patients who have intracranial hypertension because of reported effects on intracranial pressure (ICP) and cerebral blood flow (CBF). However, re-examination of ketamine is warranted because data is conflicting (69,70). The prevailing impression is that ketamine causes an increase in CBF and cerebral metabolic rate (CMRO2). This impression is not supported by the literature. Indeed, considerable diametrically opposed results have been published on these subjects. Variations in results is no doubt largely due to differences in methodology, and failure in some instances to control blood carbon dioxyde (PaCO2) may have contributed significantly to the confusion (71). Anaesthetics and the pressure of carbon dioxide in arterial blood appear to greatly influence ketamine effects on the cerebral vasculature even in conditions of prior raised ICP.

Using hypovolaemic rats as an experimental model, Longnecker and Sturgill found, in 1976, that those animals given ketamine had better survival rates than those given either halothane or barbiturates (72). As an NMDA antagonist, ketamine has been shown experimentally to have neuroprotective properties during transiant ischemia and experimental head trauma in rats (73,74). Miura et al recently put these data in doubt, showing that volatile anaesthesia was neuro-protective compared with ketamine (75), but blocking excessive NMDA-receptors stimulation may reduce progressive neuronal degeneration and cell death. In Miura study, histologic damage, in rat brains after near-complete ischemia, was not different between fentanyl and ketamine, with a lower damage with isoflurane. However, motor scores were better with ketamine as compared with fentanyl, and not different from isoflurane anaesthesia (75). Ketamine was found to protect cellular energy status after ischaemeic insults and maintained ATP production, glucose metabolism, and mitochondrial transmembrane potentials. Finally, Ketamine exhibits clear anticonvulsant properties (1,76,77). The majority of the studies that show that ICP rises on ketamine application have been carried out on spontaneously breathing animals or patients. Other authors have reported a rise in ICP on giving induction agents such as flunitrazepam and thiopental during spontaneous ventilation, although the latter is considered a potent drug for reducing ICP (78).

In 1982, Schwedler and al showed that i.v. injection of ketamine 5 mg/kg caused a significant increase in intracranial pressure from 13±3 to 19±3 mmHg in spontaneously breathing goats, but no change in ventilated goats in which PaCO2 had been controlled. Ketamine caused a sudden rise in MAP and PaCO2 in spontaneously breathing goats and CBF increased, reaching maximum values about five min after ketamine administration. Similar injection of ketamine into goats, paralysed with gallamine, caused no increase in CBF. Subanesthetic doses of ketamine (0.1-0.2 mg) injected directly into the cerebral circulation failed to produce any significant change in CBF, indicating that ketamine has no immediate or direct effect on cerebral vessels (71). Interestingly, ketamine induced a similar decrease in CMRO2 (11-15%) in the two groups until recovery. The authors concluded that CBF increases were the secondary result of increases in PaCO2 and arterial blood pressure. Anyhow, in experiments where CBF changes are correlated with changes in MAP, one might wonder about the capability of the cerebral auto-regulation, particularly in patients with cerebral vascular impairment (73). Similarly, Pfenninger et al showed in anaesthetised (N20/buprenorphine) hypovolaemic piglets (blood pressure reduced to 70% of the original value by controlled haemorrhage) in which ICP was raised by insufflation of an epidural balloon, that ketamine (0.5 and 2 mg/kg iv) led to a significant rise of ICP only in spontaneously breathing animals. In contrast, the ventilated animals showed a significant reduction in ICP. No changes in PaCO2 were observed in this group, while those piglets breathing spontaneously had dangerous PaCO2 rise. At both ketamine doses, a significant correlation could be found between the PaCO2 and the ICP. None of the ventilated piglets died during the investigation, whereas three out of ten of those animals breathing spontaneously died of apnoea. Interestingly, the MAP of the spontaneously breathing group increased slightly after ketamine, in contrast, the MAP of the ventilated animals fell significantly by 20% (73).

Albanese et al confirmed these results in eight patients with traumatic brain injury (ICP less than 25 mmHg), controlled with propofol infusion (3 mg/kg/hr) and mechanical ventilation. PaCO2 was maintained between 35-38 mmHg. Three doses of ketamine (1.5, 3 and 5 mg/kg i.v.) were associated with a small but significant decrease in ICP (18-30%, 2, 4 and 5 mmHg respectively) a few minutes after each ketamine injection. There were no significant differences in cerebral perfusion pressure, jugular vein bulb oxygen saturation and middle cerebral artery blood flow velocity, measured by transcranial Doppler ultrasonography (Vmca), and the authors hypothesised that flow remained coupled to metabolism. Moreover, Ketamine induced a low-amplitude fast-activity electroencephalogram, with marked depression, such as burst-suppression (79).

In 1995, Mayberg et al showed that Vmca decreased after iv ketamine administration (1 mg/kg) in neurosurgical patients undergoing craniotomy for excision of brain tumor or clipping of cerebral aneurysm. Al patients were anaesthetised prior to ketamine administration and were kept normocarbic to mildly hypocarbic. None of them had severe intracranial hypertension (the highest ICP was 20 mmHg), but there was a small, but significant decrease in ICP immediately after ketamine administration and a significant decrease in total EEG power. The balance between cerebral metabolism and flow was not altered (80). In 2000, Sakai et al confirmed in 38 patients without neurological complications with mechanically ventilated lungs, that ketamine administration (2 mg/kg followed by continuous infusion at 2 mg/kg/hr) during propofol anaesthesia (6 mg/kg/hr) does not affect Vmca, mean arterial pressure or heart rate or the cerebrovascular CO2 response (81). In contrast, in a randomized clinical investigation, Nagase et al found that ketamine (1 mg/kg) reduced cerebrovascular response to CO2 in humans during isoflurane anesthesia. PaCO2 was altered by supplementing the inspired gas with CO2 without changing the respiratory conditions in order to obtain hypocapnic, normocapnic, and hypercapnic conditions. Interestingly, CBF, during hypercapnic conditions, was comparable with controls (82).

In summary, these results suggest that ketamine may not adversely alter cerebral haemodynamics of mechanically ventilated head-trauma patients sedated with propofol. Ketamine has been reported to increase CBF or ICP in part because of an increase in MAP or PaCO2. But increase of CBF velocity is not blocked by maintaining MAP with esmolol, suggesting a direct effect of ketamine, presumably because ketamine induces a central nervous excitation that stimulates cerebral metabolism. The ketamine-induced increase in CBF velocity closely correlates to the increase in neuronal activity in healthy volunteers. On the contrary, ketamine decreases electroencephalogram activity in patients during propofol sedation or isoflurane/N2O anaesthesia (81) and the dramatic increase of local rates of cerebral glucose utilisation in the limbic system observed with ketamine alone is prevented by treatment with diazepam (83). Akeson et al demonstrated that midazolam, too, antagonises cerebral metabolic stimulation induced by ketamine in normoventilated pigs anaesthetised with fentanyl/N2O, and that CBF was more depressed by ketamine-midazolam than ketamine only (84).

Accordingly, most authors suggest the possibility that propofol or midazolam block ketamine-induced increase in neuronal activity, resulting in inhibition of the increase of CBF (81). We may conclude that ketamine can be given to ventilated, anaesthetised patients without adversely altering cerebral hemodynamics and may not be contra-indicated in all patients at risk for intracranial hypertension (80). When ketamine is added in a background anaesthetic, especially propofol, its property of central nervous excitation is blunted and it increases the depth of anesthesia. This is supported by the fact that the peripheral vascular stimulation often seen with ketamine is ablated, as demonstrated by the lack of increase in MAP (79).

Sedation with respect of spontaneous breathing

Sedation is used frequently in association with a wide variety of painful procedures like catheters insertions, thoracic drainage, iterative wounds dressings, reposition maneuvers or endoscopy. Even if not absolutely necessary, sedation is also often mandated during the performance of regional anaesthesia, especially painful nerve blocks or for complementary analgesia. The ideal premedicant drug would provide muscular relaxation, anterograde amnesia and complementary analgesia without significant circulatory and respiratory depression that could endanger the spontaneously breathing patient (85). Respiratory function is frequently impaired by sedation and sedation is associated with serious adverse events. Sedative agents such as barbiturates and benzodiazepines cause loss of airway muscle tone and an increase in airway resistance. In contrast, at subanesthetic doses, ketamine exerts potent analgesic and sedative properties without causing respiratory depression.

As we saw earlier, important emergence phenomena or significant changes in blood pressure or heart rate usually do not occur with low-dose ketamine, especially if careful titration is particularly looked after. The ED_{95} for abolition of response to command by ketamine is approximately 0.6 mg/kg. Ketamine should be titrated starting with very small doses, such 5-10 mg by i.v. bolus, up to 0.5 mg/kg or 0.1-0.2 mg/kg/hr i.v. Use of low-dose ketamine prior to injection of local anaesthetics has become increasingly popular for outpatient cosmetic surgical procedures (1).

Ketamine differs in several aspects from other anaesthetics. Skeletal muscle tone is maintained or even increased during ketamine anaesthesia, and even respiratory muscle seems to be affected as ketamine increases diaphragmatic contraction (86). Morel et al showed that ketamine produces an important ventilatory stimulation, with an increase in minute ventilation (VE) and stable SaO_2 (87). In contrast, Clergue et al showed that ketamine depresses the relationship between VE and end-tidal PCO_2 (P_ACO_2) and probably increases effective impedance of the respiratory system (88).

During halothane anaesthesia, both reduction of arterial oxygen tension and right-to-left shunt correlate strongly to the extent of atelectasis. Atelectasis secondary to loss of diaphragmatic muscle tone seems to be the preponderant cause of gas exchange impairment during halothane anaesthesia. In addition, halothane causes a cephalad shift of the diaphragm and a decrease of functional residual capacity (FRC) (86). Tokics et al demonstrated the absence of atelectasis and shunt during ketamine anaesthesia (3 mg/kg, then i.v. infusion of 0.1 mg/kg/min) and spontaneous breathing, and the presence of both during muscle paralysis and mechanical ventilation in patients scheduled for minor elective abdominal surgery. During ketamine anaesthesia and spontaneous breathing, VE was maintained at the same level as during the wakened state. Cardiac output (CO) and heart rate increased by 45%. The distribution of the ventilation assessed by a multiple inert gas elimination technique was similar to the wakened state. Mean dead space ventilation using a face mask increased to 46% and $PaCO_2$ increased (5.8 to 6.8 kPa). CT scanning showed small atelectasis in only one patient out of eight. The transverse intrathoracic area increased by about 10% and diaphragmatic position was unchanged. During ketamine anaesthesia with mechanical ventilation, CO decreased by 22%. VE did not differ from the previous measurements, but dead space ventilation decreased to 28% and $PaCO_2$ was lower than previous measurements. PaO_2 decreased and P_A-PaO_2 increased. Transverse intrathoracic area decreased and atelectasis in dependent lung regions appeared in seven out of eight patients. There was a correlation between atelectasis area and shunt fraction, similar to earlier findings during halothane anaesthesia, where the dimensions of the thoracic cavity are reduced by a cephalad displacement of the diaphragm and a mean reduction of transverse thoracic area. The loss of diaphragmatic tone causes a compression of lung tissue, particularly dependent regional lung volume. Differences in chest wall mechanics explain the absence of atelectasis during ketamine anaesthesia and spontaneous breathing. During barbiturate and halothane anaesthesia, atelectasis develops promptly. In contrast, gas exchange was only minimally affected by 20 min of ketamine anaesthesia (86). In 1986 Mankikian et al used non invasive measurement of chest wall movements to study qualitative information on the partitioning of tidal volume (V_T) between abdominal and rib cage compartments in male subjects during ketamine anaesthesia (3 mg/kg, then 20 µg/kg/min). Succinylcholine was injected to facilitate tracheal intubation. V_T, respiratory rate (RR) and VE remained unchanged 5 min following the recovery of spontaneous breathing. FRC (measured by the helium dilution method) increased by 10% in contrast with the classic decrease (-18%) reported either after intravenous or inhalation anaesthesia (89), and

$\Delta V_{RC}/V_T$ (the rib cage contribution to tidal breathing) increased significantly, suggesting a sparing effect of ketamine on the rib cage stability and intercostal function. FRC stability may explain a beneficial effect on gas exchange because a correlation exists between FRC during anesthesia and alveolar-arterial oxygen difference. The absence of change in PaO_2, which has been found in ketamine-anaesthetised subjects (90) is probably related to FRC stability. In contrast, halothane induces a preferential suppression of intercostal electromyographic activity, with a loss of rib cage stability characterised by an inward inspiratory movement. This effect suggests a change in chest wall shape because parasternal intercostals are essential in maintaining rib cage shape (91).

When patients are sedated with midazolam, even if they remain easily rousable, close attention must be paid to their airway, and airway support is likely to be required. In contrast, ketamine sedation is not likely to reduce airway muscle activity and impair airway patency : Drummond et al studied the EMG activity of the muscles of the tongue, anterior neck and scalene group with surface electrodes and compared it with the wakened state in male patients premedicated with temazepam. Patients were randomly allocated to receive sedation with either midazolam (median dose 5 mg, to obtain a sedated state where the eyelids were drooping but not shut, with considerable variation, independent of age) or ketamine 1 mg/kg. After ketamine, all patients became quiet and detached. No patient reported unpleasant experience. Muscle activity decreased significantly after midazolam and partial or complete airway obstruction occurred in 10 out of 12 patients, whereas after ketamine, activity did not change significantly and there were no episodes of airway obstruction (92).

Besides its beneficial effect on lung function and airway patency, ketamine provides the unique advantage of partially protecting the lung from aspiration. Previous studies in humans with ketamine 1 mg/kg reported greater resistance to aspiration of radio-opaque markers than with other sedatives such as diazepam (93). In contrast, it has been shown that subhypnotic concentrations of isoflurane or sevoflurane, and particularly propofol, cause an increased incidence of pharyngeal dysfunction (94).

Thus, ketamine may help to solve many problems with situations where a general anaesthesia is not mandated, but where analgo-sedation is necessary with preservation of spontaneous breathing, even when the anaesthesiologist works far from the operating room.

Ketamine $t_{1/2}\alpha$ (7-11 min) and $t_{1/2}\beta$ (120-180 min) are similar to the midazolam half-lives and Toft et al showed that midazolam is a more satisfactory adjunct to ketamine anaesthesia than diazepam in patients undergoing endoscopy, with a shorter time to recovery and few emergence reactions. No awareness during anaesthesia was reported (95). In 1991, Monk et al compared ketamine and alfentanil infusions in combination with midazolam for outpatients lithotripsy. They found a superiority for alfentanil in terms of calculi fragmentation, but alfentanil was associated with more episodes of hemoglobin oxygen desaturation < 90% (23% vs. 5%) and ability to recall intraoperative events (45% vs. 12%) (96). Ketamine has been advocated for complementary sedation and analgesia during regional anaesthesia. Frizelle et al showed that combining ketamine (0.1 mg/kg) to propofol (0.4 mg/kg) improved haemodynamic stability during sedation for spinal anesthesia. Arterial pressure was significantly higher than in control patients, sedated with propofol only (0.5 mg/kg) (97).

In these situations where opioid use makes it impractical to maintain the patient's SpO_2 with spontaneous ventilation, ketamine intensifies the upper airway or laryngeal reflexes, providing sedation, amnesia and analgesia and protection against aspiration. Paradoxical agitation often observed with benzodiazepines is less likely to be encountered if the physician takes the precaution of giving information to the patient prior to ketamine injection. The potentially strange sensations (colourful visions, hearing alterations, floating feelings...) must be explained and 1-2 mg midazolam injected a few min prior to beginning is highly recommended (98).

When using ketamine in spontaneously breathing patients, one must bear in mind some important rules : ketamine must be carefully titrated (boluses of 5-10 mg i.v.) because too rapid injections of too high doses may cause transient apnoea. Doses will be limited to the minimum necessary (98). In a context of full stomach, endotracheal intubation is mandated, with the imperative use of succinylcholine, because ketamine does not allow sufficient airway relaxation to perform intubation (99).

Ketamine in modern anaesthesia

When it is used as a sole anaesthetic, ketamine induces a dose-related rise in the rate-pressure product, often in excess of 100 per cent, mediated by sympathomimetic effects due to centrally mediated release of catecholamines and inhibition of their re-uptake (1). Due to the sympatho-adrenergic activation, monoanaesthesia with ketamine is recommended classically in patients with shock or cardiac tamponade (100). The effects on cardiac function are discussed, but no depressant effect seems to occur at clinically relevant concentrations (101).

Ketamine has been shown to be effective at preventing and actually reversing wheezing in patients with asthma who require anesthesia and intubation (102). Ketamine exerts a broncho-dilating effect similar to that of volatile anaesthetics, blunted by beta- blockers (1). Hirota showed in 1996 that both ketamine isomers produced equipotent relaxation in histamine-preconstricted isolated guinea pig tracheal strips (spasmolytic effect). S(+)-ketamine produced a greater potentiation of adrenaline-induced relaxation than R(-)-ketamine. Changes in intracellular Ca^{2+} level secondary to a reduction in the L-type Ca^{2+} current may partially mediate the spasmolytic effect of ketamine, because increase in extracellular Ca^{2+} significantly reduced ketamine induced relaxation (103). The increase in airway resistance with manipulation such as bronchoscopy or tracheal intubation is mediated through neural mechanisms. Brown et al demonstrated that the bronchoprotective effects of ketamine and propofol on airways is through neurally mediated mechanisms and that ketamine is more potent than propofol at preventing neurally induced bronchoconstriction. An infusion of propofol and ketamine, but not thiopental, into the bronchial artery of anaesthetised sheep, caused a dose-dependent lowering of a vagal nerve stimulation-induced bronchoconstriction (104). Anyway, the recognition of a high incidence of unpleasant side effects such as emergence reactions and cardiovascular excitability certainly limited the use of racemic ketamic as the sole analgesic in anaesthesia. On the other hand, a wide variety of adjunct drugs have been proposed to partially or totally reduce side effects : thiopental, droperidol (105), diazepam, midazolam, esmolol (106) or clonidine (107). Above all, propofol can truly eliminate the side effects of ketamine (108).

Combining ketamine with propofol

In 1991, Guit et al compared the combinations propofol-fentanyl and propofol-ketamine in a double blinded, prospective study of 18 patients who underwent noncardiac surgery. Propofol-ketamine anaesthesia was characterised by stable arterial pressure throughout the operative period, compared to the lower blood pressure found in the patients given propofol-fentanyl (108). Anaesthesia was induced with propofol 2 mg/kg and either fentanyl (3 µg/kg) or ketamine (1 mg/kg). Anaesthesia was maintained with propofol 12 mg/kg/hr during the first 30 minutes, followed by 9 mg/kg/hr for 30 minutes and then 6 mg/kg/hr combined with fentanyl 1.5 µg/kg/h or with ketamine 2 mg/kg/h. Vecuronium was administered and the patient's lungs were ventilated with oxygen-enriched air with an FiO_2 of 0.35. The continuous administration of drugs was stopped at the end of surgery. Stable arterial pressure and heart rate were seen in the patients who received propofol-ketamine, except for a temporary increase directly after tracheal intubation. Systolic pressure increased by 13% and heart rate by 14%. No extra analgesics were required in the propofol-ketamine group, but patients who received propofol-fentanyl required a mean additional dose of fentanyl 0.72 µg/kg/hr. Patients who received propofol-ketamine demonstrated a significantly longer recovery time than patients given propofol-fentanyl (time to awakening 22 ± 23 vs. 9 ± 10 minutes). There were increased incidences of dizziness and confusion (33 vs. 11%) but in all cases, the confusion was judged to be minor. No patient reported dreaming after surgery and all patients judged the propofol-ketamine combination to be pleasant compared to 90% of the patients with propofol-fentanyl. No NVPO were experienced in the propofol-ketamine group vs. 11% with propofol-fentanyl (108). In 1991, too, Doenicke et al compared two groups of patients receiving either fentanyl or ketamine as the sole analgesic. A pharmacocinetic model served to design the rate of administration of ketamine : initial bolus of 38 mg followed by infusions of 42, 35, 32 and 28 mg every 30 min. The ketamine infusion was stopped 15 min before the end of procedure. Fentanyl was given in 200 µg and then 100 µg boluses, with the last administration 3 min before the end of procedure. Propofol was infused 6.6 mg/kg/hr in the fentanyl group, and 8.4 mg/kg/hr in the ketamine group. Here too, propofol-ketamine anaesthesia was characterised by stable and higher arterial pressure throughout the operative period, compared to the lower and unstable blood pressure (peaks) found in the patients given propofol-fentanyl. Patients given ketamine were better aroused and experienced no hallucinations in the recovery room. One of them needed an analgesic, compared to seven of the ten patients in the fentanyl group (109).

The hypnotic and anaesthetic effects of propofol are thought to be principally via actions at the $GABA_A$ receptor at a site distinct from the benzodiazepine and thiopental sites. Hui et al demonstrated in 1995 that ketamine and propofol have additive interactions when half the hypnotic ED_{50} of ketamine is combined with half the hypnotic ED_{50} for propofol. They showed that ketamine does not significantly alter the ED_{50} for apnoea of propofol and that the cardio-stimulant effects of ketamine balanced the cardio-depressant effects of propofol. The arterial pressure and heart rate effects of the individual agents (the sympathetic effects of ketamine and the vagotonic effects of propofol) tended to cancel each other out, resulting in improved cardiovascular stability. They found that ED_{50} at the hypnotic endpoint is 0.4 mg/kg for ketamine alone, but 0.2 mg ketamine in combination with 0.6 mg/g propofol, and that ED_{50} at the anaesthetic endpoint is 0.7 mg/kg for ketamine alone but 0.35 mg ketamine in combination with 1 mg/kg propofol (110).

Recently, Friedberg reported an anecdotal series of 2059 elective plastic procedures performed with office anaesthesia, using the propofol-ketamine technique as a room air, spontaneous ventilation, intravenous dissociative anaesthetic technique. Patients received midazolam and glycopyrrolate as premedicant drugs. The propofol infusion was titrated until loss of verbal contact occurred and lid reflex disappeared. Once hypnosis was achieved, a bolus dose of 50 mg ketamine was administered. If the patient made purposeful movements in response to the local anaesthetic, a second dose of ketamine (25-50 mg) was administered. The patients were maintained on the infusion of propofol until the termination of the procedure. Average surgery time was 153 min and patients consumed an average 10 mg/min of propofol and 200 mg or less total ketamine. In this 5-year series, 99% of patients maintained a SpO_2 > 90% breathing room air spontaneously. No hallucination was reported and less than 1% of patients reported pleasant and typically colorful dreams. The majority of patients regained consciousness in 10-15 min after discontinuation of the propofol infusion and were discharged to home alert by the end of the first postoperative hour. A near zero PONV rate (0.6%) was observed along with universal patient satisfaction (111). In 2000, Badrinath et al demonstrated in a randomised, double-blinded placebo-controlled study, that propofol (90 µg/kg/min) in combination with ketamine (18 µg/kg/min), was the ideal drug regimen in female outpatients undergoing breast biopsy procedures under local anaesthesia, with no need for opioid supplementation, no increase in PONV psychomimetic side effects incidence or in delay of discharge times (112).

It finally appears that propofol-ketamine anaesthesia provides multiple advanta-ges (111,1) :

- no need for N2O (100 per cent oxygen can be utilised) or scavenging considerations for exhaled gases and vapors, non-triggering agents for malignant hyperthermia.
- propofol and ketamine share mutually complementary pharmacologic properties : propofol blunts cerebral and cardiovascular exciting properties of ketamine, has significant anti-emetic properties and euphoriogenic qualities as well, and prevents ketamine-induced hallucinations. Ketamine exhibits significant analgesic properties with no need for supplemental opioids.
- stable haemodynamics, post-operative respiratory security.
- positive cost : benefit ratio

Combining propofol and ketamine exhibits even more advantages : Hess et al found fewer ventricular rhythm disturbances with propofol-ketamine for anesthesia and perioperative sedation than with high dose fentanyl and benzodiazepine in patients who underwent aortocoronary bypass surgery. Ketamine which resembles cocaine in the chemical structure, inhibits the neuronal uptake of catecholamines like cocaine and acts as a sodium-channel blocker (38), one of the ways how antiarrhythmic drugs work (113).

Some « tricks » must be kept in mind when using the propofol-ketamine combination. Injecting 10 mg ketamine prior to the injection of propofol may diminish the pain experienced by patients (114). Ketamine is more lipid soluble than thiopentone ; in order to prevent delays in emergence time, injections must be limited as necessary : patient movement doesn't mean patient awareness. The reported ED_{50} for the abolition of response to painful stimulation is 1.3 mg/kg. Ketamine administration must be stopped 20 to 40 min before the expected end of surgery. The longer the duration of surgery, the earlier the ketamine stops (98). Salivary and tracheal-bronchial mucus gland secretions are increased by ketamine, necessitating prophylactic administration of an antisialogogue. One should not assume that the use of ketamine avoids the need for careful airway management and/or endotracheal intubation in all situations (1,99).

With respect to the recent development of modern anaesthesia, two points merit further consideration : first, in the future, not only propofol, but ketamine itself may be administered with target controlled infusion for TIVA (18,115,116,117,118). Second, in contrast to other anaesthetic agents, BIS cannot be used to monitor hypnosis during ketamine anaesthesia, because of its excitatory effects on the EEG (119,120). Sakai et al showed that the decrease in BIS values are less in patients receiving propofol-ketamine compared to propofol alone (121), but Madei et al. recently demonstrated that appropriate utilisation of BIS monitoring could help reduce the time to extubation, following the conclusion of surgery during propofol-ketamine anaesthesia (122).

Ketamine and anaesthesia on the battle field

Because of the above various favourable properties, ketamine appears as an anaesthetic of choice for military surgery (123). Battle casualties are characterised by a great number of shocked patients with multiple lesions and full-stomach, limited preoperative evaluation and lack of supply. Early surgery is primarily intended for haemostasis. Hypotensive victims must be quickly resuscitated and systematic tracheal intubation must be performed with rapid sequence induction avoiding cardiovascular collapse. Early anesthesic recovery is mandatory and patients must be able to maintain a clear airway as soon as possible. Better oxygen delivery and survival after ketamine anesthesia have been reported in experimental models of haemorrhage (124). NMDA receptor-channel non competitive blocking and anticonvulsant properties make it particularly suitable for induction and maintenance of anesthesia in patients with head injury, and in patients exposed to organophosphorus compounds (123). Analgesic properties outlasting the period of anesthesia, even at subanesthetic doses, permit intra and post-operative analgesia without the need for morphinomimetics. The uselessness of supplementation by nitrous oxide, no respiratory depression with higher PaO_2 values, when compared to halothane, makes it particularly safe for analgesia during surgical procedures far from the operating theatre. As we saw, in combination with propofol, ketamine anaesthesia allow abdominal and orthopaedic surgery without the need for opioids (108,123). Mion et al proposed inducing anaesthesia with propofol 2 mg/kg and ketamine 1 mg/kg, with maintenance of anaesthesia with ketamine 2 mg/kg/h and propofol in regressive doses (12, 9 and 6 mg/kg/h) (123). Combining ketamine with midazolam, a water-soluble benzo-diazepine possessing a pharmacokinetic profile similar to that of ketamine would produce an ideal i.v. combination (1). Restall proposed administering midazolam 0,07 mg/ kg combined with ketamine 1 mg/kg with tracheal intubation, facilitated with vecuronium. Maintenance of anaesthesia would be provided with a mixture of ketamine 200 mg, midazolam 5 mg and vecuronium 12 mg in 50 mL saline, administered to a rate in mL/h corresponding to half of the patients body weight (in Kg) (125). The intramuscular route is also appropriate (12 mg/kg), notably to perform an amputation when a life-saving disengagement of a trapped patient with no intravenous access is unavoidable. In case of shock, anaesthetic requirements are decreased (126), and induction must be performed with ketamine alone. Propofol is introduced when haemodynamics are under control (123).

Ketamine for analgo-sedation in the intensive care unit

Sedatives continue to be used on a routine basis in critically ill patients. Although many agents are available and some approach an ideal, none are perfect. Patients require continuous reassessment of their pain and need for sedation. Pathophysiologic abnormalities that cause agitation, confusion, or delirium must be identified and treated before unilateral administration of potent sedative agents that may mask potentially lethal insufficiencies. The routine use of standardised and validated sedation scales and monitors is needed. It is hoped that reliable objective monitors of patients' level of consciousness and comfort will be forthcoming. Ketamine seems to have a place in the ICU pharmacologic armamentarium to ensure the safe and comfortable delivery of care (68, 128). Ketamine, especially in combination with midazolam or propofol, is useful for sedation in intensive care units. These combinations have weaker sympathomimetic and general endocrine-stimulating properties, and must be re-evaluated in patients classically contra-indicated for ketamine use, those who lack normal intracranial compliance or who have significant myocardial ischemia (68).

Ketamine has privileged indications for sedation of asthmatic patients admitted to an intensive care unit (129). Petrillo et al showed in patients with an acute exacerbation of asthma, who were unresponsive to standard therapy, that addition of ketamine (1 mg/kg i.v., followed by a continuous infusion of 0.75 mg/kg/hr) to standard therapy was associated with improved scores of acute asthma severity. Oxygen saturation significantly improved after ketamine infusion and side effects were transitory (130).

A reduction of exogenous catecholamine demand can be expected in patients with cardiovascular instability and exogenous catecholamine requirements : in surgical intensive care patients, Adams et al showed that higher levels of ADH and noradrenaline during S(+)-ketamine-midazolam analgosedation (K/M) compared to S(+)-ketamine-propofol analgosedation (K/P) allow us to expect higher cardiocirculatory stability (131). Patients with initial cardiocirculatory stability received 0.33-1.0 mg/kg/h S(+)-ketamine together with 1-3 mg/kg/h propofol, whereas patients with impaired cardiocirculatory stability received 0.33-1.0 mg/kg/h S(+)-ketamine and 0.033-0.1 mg/kg/h midazolam. The endocrine stress response was reduced by both regimens : ADH, ACTH and cortisol decreased during the observation period. K/P showed some advantages over K/M with respect to control and quality (16 h after start of analgo-sedation, 93% of patients in the K/P-group were immediately cooperative vs. 64% in the K/M). Systolic arterial pressure was comparable, whereas heart rate was significantly lower in the K/P-group. In a prospectively randomised study in ventilated patients subject to treatment with catecholamines (epinephrine or norepinephrine), and sedated with 2.5 mg/h midazolam, Adams et al showed that mean catecholamine dosage decreased by13% in the ketamine group (infusion of 50 mg/h ketamine) compared to a significant increase by 33% in the fentanyl group (0.2 mg/h fentanyl). Haemodynamics (MAP, heart rate, cardiac index, pulmonary capillary wedge pressure, and shunt volume) were comparable in both groups, but pulmonary artery pressure and central venous pressure increased in the ketamine group but not in the fentanyl group (132).

There is increasing evidence that ketamine may be valuable for septic patients. Hofbauer et al. showed in 1998 that ketamine reduces the migration of leukocytes through endothelial cell monolayers in a dose-dependant manner. Ketamine inhibits the function of leukocytes more than the function of endothelial cells (133).

Taniguchi et al. suggested that ketamine may offer advantages in endotoxemia. They showed in a rat model that ketamine pretreatment abolishes endotoxin-induced hypotension and inhibits the increase in plasma concentrations of tumor necrosis factor α and interleukin 6. Post-treatment was less effective, but remained superior to saline (control group) (134).

Moreover, the effects of ketamine on intestinal motility are probably of interest in the ill-fed patients, compared to opioid sedation : postoperative intestinal atonia is a complication which is likely to occur in patients predisposed to constipation and in patients after intra-abdominal operations. The postoperative delay of bowel movement is diminished when ketamine is preferred to opioids. Using the H_2 exhalation test, Freye et al showed no inhibition of intestinal motility following ketamine-midazolam anesthesia, compared to fentanyl-midazolam anaesthetic technique. The gastro-intestinal inhibition, after the opioid-based anaesthetic technique, was significantly prolonged : mean gastro-coecal transit time was 210 min following ketamine-midazolam vs. 302 min following fentanyl-midazolam anaesthesia (135,136).

Kawamata et al. studied the clinical effects and pharmacokinetics of ketamine and midazolam, administered continuously for prolonged sedation in critically ill patients under mechanical ventilation. Ketamine and midazolam were administered intravenously until slow response to loud verbal commands. The plasma concentrations of ketamine were analysed using high performance liquid chromatography. The mean maintenance doses of ketamine and midazolam were 2.25 ± 0.61 mg/kg/hr and 0.11 ± 0.05 mg/kg/hr respectively. There were no significant changes in blood pressure or heart rate before and after the injection of ketamine and midazolam in all the patients. The plasma concentrations of ketamine and midazolam were 3 ± 0.2 micrograms/mL and 494 ± 67 ng/mL, respectively. The time to clear response to verbal commands after cessation of the continuous infusion was 168 ± 109 min. The plasma concentrations of ketamine, and midazolam, decreased rapidly, and plasma half-life of ketamine was about 1 hour and for midazolam less than 2 hours (137). Tsubo et al recently assessed the effect of continuous hemodiafiltration (CHDF) on ketamine and midazolam kinetics in adult patients with multiple organ dysfunction syndrome. CHDF did not affect the sedation using ketamine and midazolam. There were no changes in Ramsay Sedation Score or Glasgow Coma Scale. Midazolam was not eliminated during CHDF, and small fractions of ketamine and norketamine were eliminated during CHDF. The clearance values for ketamine and norketamine were 11 ± 7 and 11 ± 12 mL/min and their daily extractions were 21 ± 7 and 10 ± 12 mg/day, respectively (138).

Clinical superiority of S(+)-ketamine : no doubt !

After stereospecific separation, the right-handed S(+)-isomer is now clinically available, notably in Germany (139,140). Pharmacological investigations show differences between those enantiomers in both qualitative and quantitative properties. The main problems associated with the ketamine racemate in clinical use are undesirable psychological dysfunction and a prolonged period of arousal. Furthermore, clinical superiority of S(+)-ketamine has been described in different therapeutic studies with regard to anaesthetic potency, extent of analgesia, effects and side effects during and after the operation, and undesirable psychological dysfunction. S(+)-ketamine has a two to four-fold higher affinity for the phencyclidine receptor of the NMDA receptor complex than the left-handed R(-)-ketamine (4). This difference results in the clinical analgesic potency of S(+)-ketamine which is two times higher in comparison with racemic ketamine. Sympathoadrenergic and haemodynamic effects of S(+)-ketamine and racemic ketamine are generally identical (141). As a sole anaesthetic agent, significant clinical progress can be expected, due to improved recovery and reduced substance load, when racemic ketamine is replaced by S(+)-ketamine. Classical side effects after ketamine anesthesia (amnesia, altered short-term memory, decreased ability to concentrate, decreased vigilance, altered cognitive performance, hallucinations, nightmares, nausea and vomiting) are clearly related to the ketamine plasma concentration (racemic mixture). Healthy volunteers recently received intravenous equianalgesic small-dose S(+), R(-) and racemic ketamine (0.5 mg/kg racemic, 0.25 mg/kg, S(+), and 1.0 mg/kg R(-)-ketamine) in a prospective, randomised, double-blind, crossover study. Transient increases in blood pressure, heart rate, and catecholamines were similar after administration of all drugs, but ketamine isomers induced less tiredness and cognitive impairment than racemic ketamine. In addition, S(+)-ketamine caused less decline in concentration, capacity and primary memory (142). Because S(+)-ketamine allows the use of significant smaller doses, the recovery phase is clearly shorter after S(+)-ketamine compared to racemic ketamine (143). S(+)-ketamine has, in several other aspects, potentially interesting properties. It has, for instance, weaker vaso-dilating properties than R(-)-ketamine (144). Moreover, increasing evidence supports a remarkable neuroprotective effect of S(+)-ketamine, which may become a promising drug for new therapeutic approaches to neuroprotection.

Conclusion

In the light of recent advances in the knowledge concerning ketamine, the classic absolute and relative contra-indications of ketamine (insufficient or untreated arterial hypertension, preeclampsia and eclampsia, insufficient or untreated hyperthyreosis, instable angina pectoris or myocardial infarction within the last 6 months, elevated cranial pressure, elevated intraocular pressure (glaucoma) and perforating ocular injuries, surgical procedures in the upper respiratory tract) have certainly to be re-evaluated in every single case, especially in emergency cases. The judicious combination of ketamine with either midazolam or propofol is clearly able to blunt haemodynamic systemic and intracranial reactions that have been the rationale for ketamine contra-indications.

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Contact : Gérard Zappavigna

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org : membre du comité d'organisation ; Corr : correspondant pour la structure d'exercice, membre de droit du conseil d'administration

ADAM	Jean-Claude	MP	HIA Clermont Tonnerre	adam.jc@wanadoo.f	org
ALBARELLO	Sergio	MDA	Matignon		
AUBERT	Michel	MG	HIA Laveran	mvie@planete.fr	
AUBOUIN	Jean-Philippe	MC	HIA Clermont Tonnerre		
AUSSET	Sylvain	MDA	EASSA	mvie@planete.fr	
AVARGUES	Patrick	MP	HIA Bégin	patrick.avargues@mageos.com	org
BARGUES	Laurent	MP	HIA Percy	bargol@aol.com	
BENEFICE	Serge	MC	HIA Sainte Anne	benef_sa@club-internet.fr	
BENES	Nicolas	MP	CPIS	nbenes@club-internet.fr	
BENETEAU	Edwige	IADE	HIA Bégin		
BENHAIM	Jean-Marc	Dr	H A. Paré	jmbenhaiem@wanadoo.fr	
BENOIS	Alain	MDA	EASSA	alainbenois@wanadoo.fr	org
BIRON	René	MC(ER)	Bourgoin		
BLOTTIAUX	Emmanuel	MDA	BSPP		
BODENAN	Patrice	PH	CH Juvisy sur Orge	pbodenan@club-internet.fr	
BONSIGNOUR	Jean Pierre	MG	INI		
BORET	Henry	MDA	HIA Legouest	hialegoust.daru@wanadoo.fr	
BORNE	Marc	MP	HIA Val de Grâce	MARC.BORNE@wanadoo.fr	
BOULLAND	Pascal	MP	Hia Legouest	pascalboulland@wanadoo.fr	
BOURRE	Anne-Marie	MP	HIA Legouest		
BRINQUIN	Louis	MCS	HIA Val de Grâce		
CAMPILLO	Alexis	MC	BMPM	alexcam@wanadoo.fr	
CARPENTIER	Jean Pierre	MC	HIA Laveran	daru.laveran@wanadoo.fr	
CARRAS	Pierre-Marie	Dr	Croix St Simon	pcarras@wanadoo.fr	
CARSIN	Hervé	MCS	HIA Percy	ctbpercy@club-internet.fr	
CHANI	Mohammed	MCdt	Libreville	chani.mohamed@caramail.com	corr
CHASSAING	François	MP	HIA Legouest	hialegouest.daru@wanadoo.fr	corr
CHAZALON	Pascal	MDA	EASSA	pchzlu@club-internet.fr	
CHEVARIN	***merci de nous contacter pour compléter votre adresse***				
CHEVRE	Arnaud	MDA	Présidence	arnaud.chevre@free.fr	
COMBES	Laurent	MP	BMPM	combes.laurent@free.fr	
CORDEBAR	Régis	Dr	CH Pontivy	regis.cordebar@wanadoo.fr	
CURET	Pierre-Marie	MP	HIA Sainte-Anne	pimacuret@wanadoo.fr	
D'ANDIGNE	Eric	MDA	1°RPIMa	eric.da ndigne@libertysurf.fr	
De SAINT-MAURICE	Guillaume	MDA	EASSA	gdesaintmaurice@mogros.com	
DEBIEN	Bruno	MP	HIA Percy	brunodebien@voila.fr	
DELORT	Guillaume	MP	SAU HIA Bégin		
DEROUDILHE	Gilles	MP	HIA Robert Picqué	gilles.deroudilhe1@fnac.net	
DESCANLERS	Christian	MP	BSPP	christian.decanlers@libertysurf.fr	
DESCRAQUES	Christian	MP	HIA Bégin	deschris@aol.fr	org
DESLANDES	Jean Claude	Dr	"Urgence Pratique"	urgencep@mnet.fr	
DOPPIA	Max-André	Dr	CHU Caen	doppia-ma@chu-caen.fr	
DOROL	Jack	MC	HIA Percy	tedeji@yahoo.fr	
ESCARMENT	Jacques	MC	HIA Desgenettes		
ETIENNE	Jean-Claude	***merci de nous contacter pour compléter votre adresse***			
FABBRI	Joël	Dr	Sdis 13	fabbri.joel@freesurf.fr	
FERNANDEZ	Christophe		CISAT	chrfernandez@aol.com	
FEVRE	Guillaume	MP	EASSA	glmfevre@club-internet.fr	
FONTAINE	Bruno	MP	HIA Desgenettes	bfont1@club-internet.fr	corr
FORTIN	Jean-Luc	MP	BSPP	fortin.jeanluc@free.fr	
FOUREL	Didier	MP	CTB	didier.fourel@wanadoo.fr	
FUILLA	Claude	MC	HIA Legouest	claude.fuilla@wanadoo.fr	
GIOCANTI	Jean-Pascal	MP	BSPP	jpgioc@club-internet.fr	
GIRAUD	Didier	MP	HIA Bégin	dgiraud2001@yahoo.fr	
GNAHO	Alexandre	MDA	HIA Bégin	alexandre.gnaho@worldonline.fr	
GNANGNON	Albert	MC	Cotonou	Fax : (229) 304238	corr
GOATER	Philippe	MC	HIA Val de Grâce		
GOUTTIERE	Hélène	MP	HIA Percy		
GOYFFON	Max	Dr	Muséum Histoire Nat	mgoyffon@easynet.fr	
GRASSER	Laurent	MDA	INI		
HENNEQUIN	Claude	MC (CR)	CH Blois	chennequin@ch-blois.rss.fr	
HERTGEN	Patrick	Dr	BSPP	patrick.hertgen@bspp.net	
HERVE	Yann	MDA(TA)	HIA Robert Picqué	herve.yann@infonie.fr	
HYRIEN	Jean-Paul	MP	Présidence de la Rep.	Hyrienjp@yahoo.fr	
JONIO	Véronique	MDA	BMPM	v.jonio@free.fr	
JULIEN	Henri	MG	ENSSAT	julien.hf@wanadoo.fr	corr

KAISER	Eric	MP	HIA Sainte Anne		
KALFON	Claude	MCS	DSS RA Atlantique		
KEITA	Adama Matene	Dr	Balou Sénégal		
KOULMANN	Pierre	MP	EASSA	pierre.koulmann@9online.fr	
KOWALSKI	Jean-Jacques	MC	BSPP	medecinchef.brigade@pompiersparis.fr	
KUTTLER	Jean	MC(CR)	H Pasteur Colmar	i.kuttler@rmcnet.fr	
LABADIE	Philippe	MDA	HIA Robert Picqué	Ph.LABADIE@wanadoo.fr	
LAMBERT	Evelyne	MP	EASSA		
LAPLACE	Eric	MP	HIA Desgenette	elap@orange.fr	
LE BERRE	Jean	MG	HP Dakar		
LE DANTEC	Pierre	MC	Hôpital Principal Dakar	ledantec@sentoo.sn	
LE DREFF	Pierre	MC	1° Ministre	p.le-dreff@cab.pm.gouv.f r	
LE HOT	Henri	MP	1er Rima	hlehot@club-internet.fr	
LE MAREC	Christian	MC	HIA Bégin	christian.le-marec@wanadoo.fr	org
LENOIR	Bernard	MC	HIA Percy	bsp.lenoir@wanadoo.fr	org
LEUSSIER	Jean-José	MC	HIA Laveran	daru.laveran@wanadoo.fr	
LEVECQUE	Jean-Paul	MP	EASSA	fredejp.levecque@wanadoo.fr	
LEYRAL	Jérome		BMPM	gwejerey@mageos.com	
LOUPIAC	Eric	MP	BSPP	eloupiac@club-internet.fr	
MAESTRIPIERI	Bruno	MP	La Réunion	bruno.maestripieri@wanadoo.fr	
MALGRAS	Guy	MC	Dir Def sécurité civile	guy.malgras@interieur.gouv.fr	
MAPATE	Seck	Dr	Sce Anesthésie HP Dakar		
MARTIN	Yves-Noël	MCS	HIA Bégin		
MERAT	Stéphane	MDA	EASSA	Smerat@aol.com	
MERLE	Benois	IADE	HIA Val de Grace	benoitmerle@yahoo.fr	
MEURGEY	Frédéric	MC	BSPP	mpfmeurgey@aol.com	
MEYRAN	Daniel	MC	BMPM	meyran@worldnet.fr	corr
MION	Georges	MC	HIA Bégin	georges.mion@wanadoo.fr	org
MORELL	Eric	MP	EASSA		
MORIZET	Pierre	MP	HIA Begin	morizet@club-internet.fr	
MOUGEOLLE	Claude		Sdis 49	claude.mougeolle@wanadoo.fr	
MOULINIE	Jean-Pierre	MC (CR)	IMM	jean-pierre.moulinie@imm.fr	corr
MOUROU	Hervé	MP	2°RH	hmourou@ibm.net	
OUEDRAOGO	Nazinigouba	Dr	Ouagadougou	nazinigouba@hotmail.com	
PAILLET	Pierre	MP	SM Nogent le Rotrou	paillet.pierre@wanadoo.fr	
PALMIER	Bruno	MC	HIA Sainte Anne	Bpalmier@aol.com	
PARIS	Alain	MP	HIA Percy	a.paris@voila.fr	corr
PATRIGEON	René Gilles	MC	HIA Desgenettes	rg-patrigeon@aol.com	
PATS	Bruno	MC	HIA Percy	bruno.pats@wanadoo.fr	
PELLETIER	Christophe	MDA	EASSA	pelletier.c@worldonline.fr	
PENINON	Damien	IADE	HIA Bégin	peninon.family@wanadoo.fr	
PERRY	Philippe	MP	BSPP	medecinchef.gds@pompiersparis.fr	
PETIT	Dominique	MC	HIA Sainte Anne		
PETIT	Marie-Pascale	MP	BSPP		
PETITCOLIN	Pierre Bernard	MP (CR)	Limoges	pierre_bernard.petitcolin@voila.fr	
PETITJEANS	Fabrice	MP	EASSA	cpetitjeans@wanadoo.fr	org
PETROGNANI	Roland	MC	HIA Laveran	PETROG@wanadoo.fr	
PEYTEL	Eric	MP	HIA Laveran	eric.peytel@wanadoo.fr	
POULIQUEN	Gilbert	MC	HIA Laveran	daru.laveran@wanadoo.fr	
PUIDUPIN	Marc	MP	HIA Bouffard	marc.puidupin@libertysurf.fr	
QUINOT	Jean-François	MCS	HIA Sainte Anne	jfq@club-internet.fr	corr
ROUSSEAU	Jean-Marie	MC	HIA Val de Grâce	jmrousseau@club-internet.fr	corr
ROUVIER	Bernard	MCS	Inspection SM		
ROUVIN	Bruno	MC	HIA Bégin		
RÜTTIMANN	Michel	MC	BSPP	mrutti@club-internet.fr	corr
SABY	René	MDA	HIA Laveran	daru.laveran@wanadoo.fr	
SAILLIOL	Pierre	MP	HIA Bégin	Pierresaillol@aol.com	
SAISSY	Jean-Marie	MCS	HIA Bégin	jmsaissy@aol.fr	
SALA	Jean Pierre	MC(CR)	PC Vauban Livry Gargan		
SALLE	Michel	MC	HIA Desgenettes	sallem@club-internet.fr	
SERGENT	Hervé	MP	HIA Clermont Tonnerre	h.sergent@wanadoo.fr	
SIAH	Samir	MCdt	HMI Mohamed V Rabat		
SUPPINI	Alain	MP	HIA Robert Picqué	asuppini@wanadoo.fr	corr
THEOBALD	Xavier	MC	HP Dakar	theobald@sentoo.sn	
TOPIN	François	MP	HIA Laveran		
TORTOSA	Jean Christophe	MP	HIA Bégin	JCTorto@aol.com	
TOURTIER	Jean-Pierre	MP	EASSA		
TRIFOT	Michel	MC	HIA Desgenettes		
VAGOST	Axelle	IADE	HIA Bégin		
VASSAS	Alain	MP	BA 123 Orléans		
VILLEVIEILLE	Thierry	MP	EASSA	twe@wordonline.fr	org
VINCENTI	Isabelle	MP	HIA Val de Grâce		
VITRIS	Michel	Pr	Clinique Pont de Chaume	v.mich@wanadoo.fr	
VOLOT	François	MP (CR)	CHU Dijon	francois.volot@chu-dijon.fr	