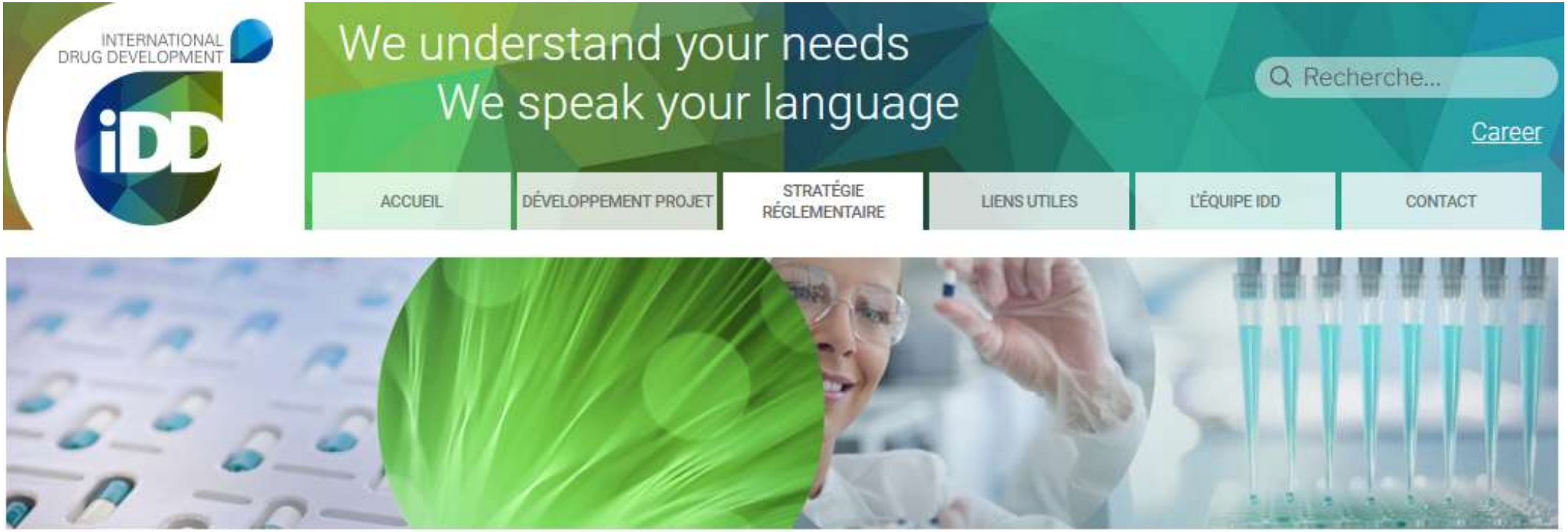
Eskétamine

Georges Mion

Hôpital Cochin

Paris

Georges Mion est consultant pour International Drug Development (IDD)



EXPLOITATION ET STRATÉGIE RÉGLEMENTAIRE

Notre cœur de métier : le dossier d'AMM

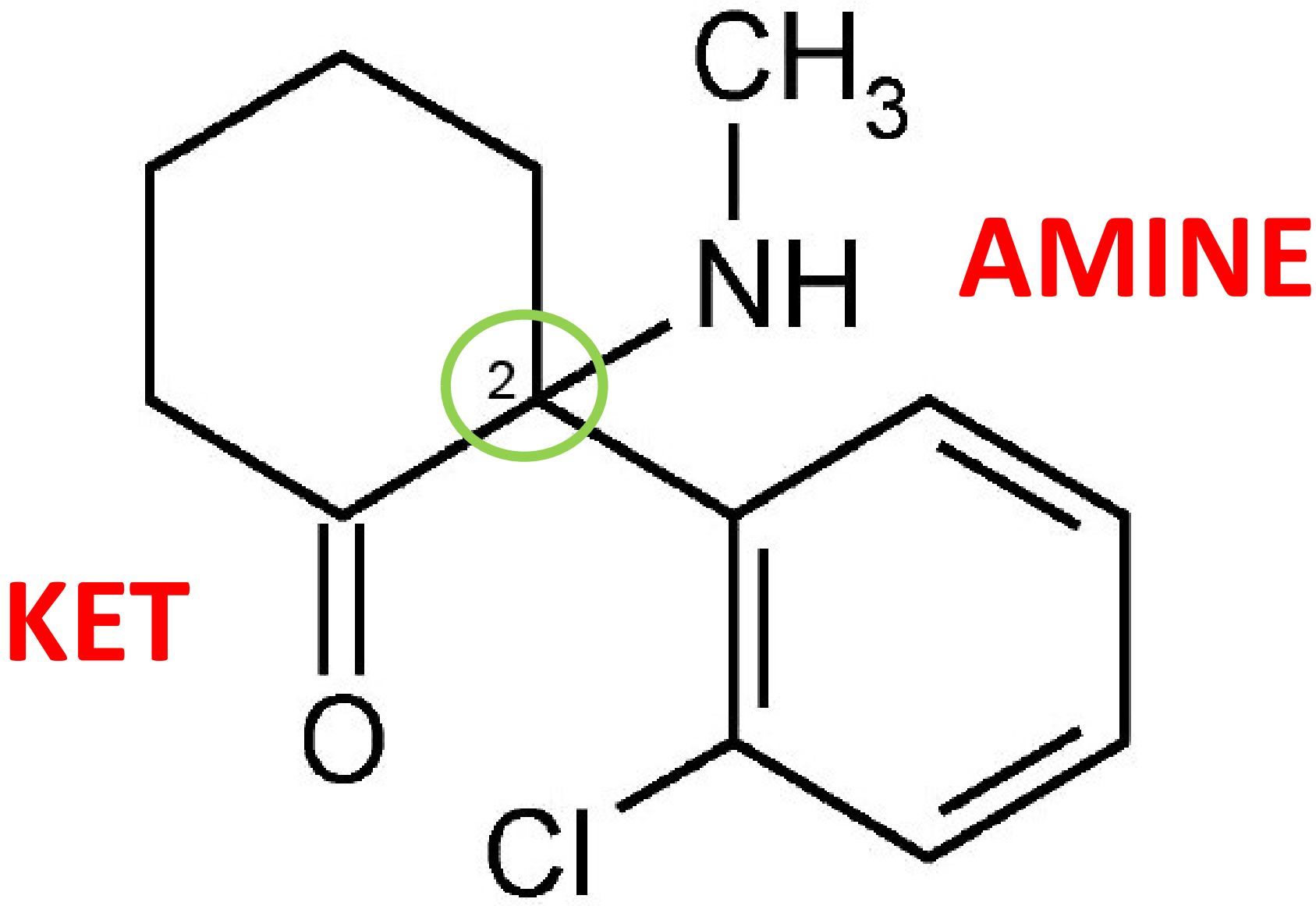
Calvin Stevens (1923-2014)

professeur de chimie à l'université de Wayne (Michigan)

synthétise le CI-581

aux laboratoires Parke Devis

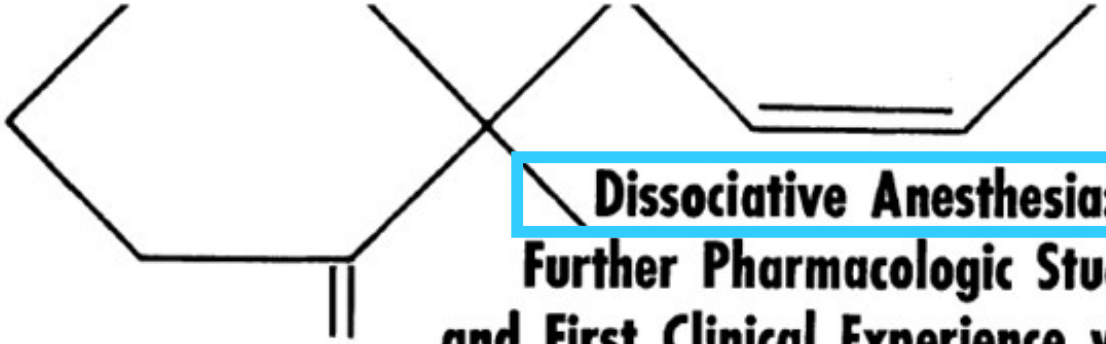
2 - ortho-chlorophényl - 2 - méthylamino - cyclohexanone



Edward F. Domino, Ph.D. (1924–2021)

Années 60

ANESTHESIA and ANALGESIA VOL. 45, NO. 1 1966



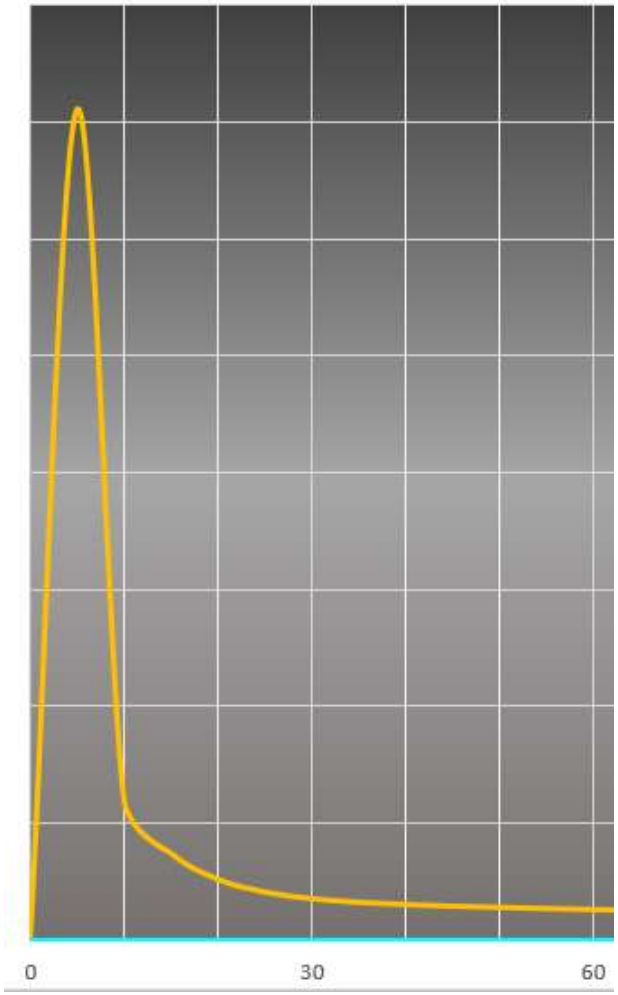
Dissociative Anesthesia: Further Pharmacologic Studies and First Clinical Experience with the Phencyclidine Derivative CI-581

GUENTER CORSSEN, M.D.
EDWARD F. DOMINO, M.D.
Ann Arbor, Michigan*

ANESTHESIE « DISSOCIATIVE »

Pharmacocinétique

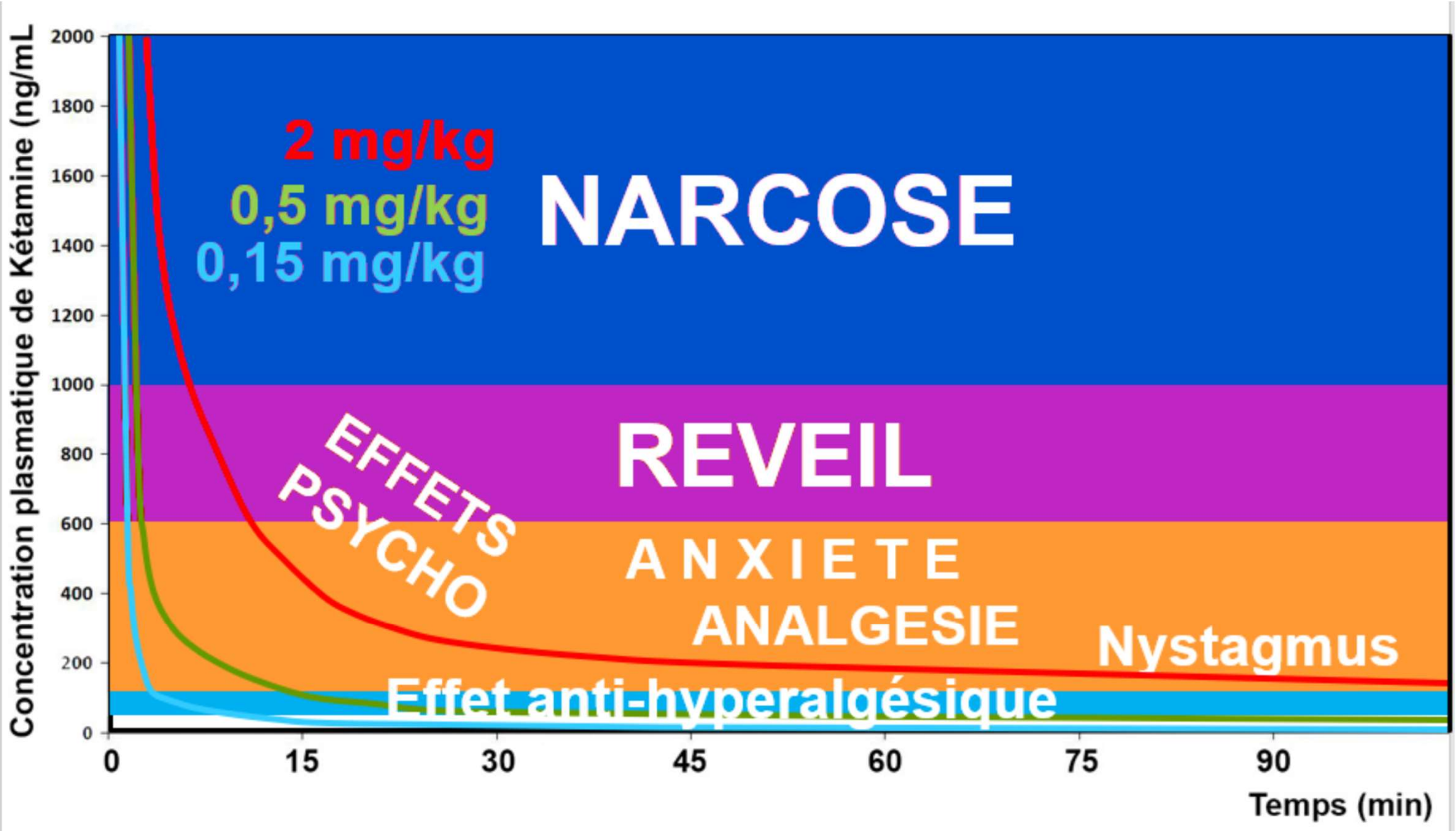
- $t_{1/2}$ α : 10 min
- délai d'action : 1 min
- $t_{1/2}$ β : 1-2 h
- Métabolisme hépatique
  - Cytochrome P450
  - premier passage
  - NOR-kétamine



Pharmacodynamie

- **Inhibition** non compétitive **NMDA-R**
- **Inhibition** des canaux **HCN1** (I*h*)
- **Effet anticholinergique central** (SAC)
- **Anticalcique** (dilatation bronches et vaisseaux)
- **Activation syst. monoaminergiques desc.**
- **Effet anesthésique local** (canaux sodiques)
- **Effets anti-proinflammatoires** (**NfκB**)
- **Effets antidépresseurs**

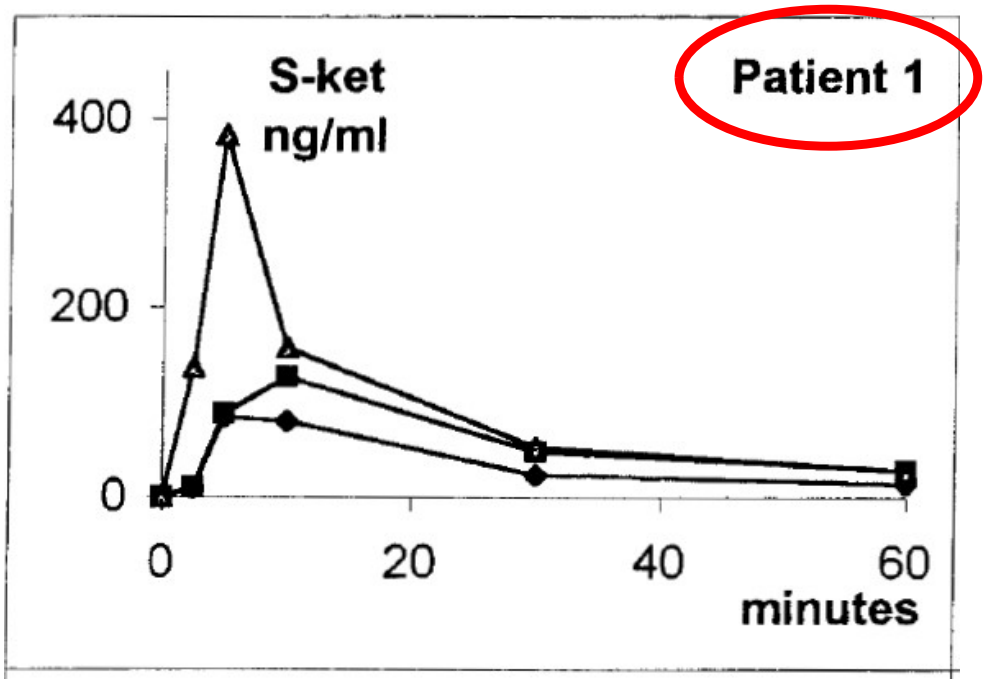
Racémique

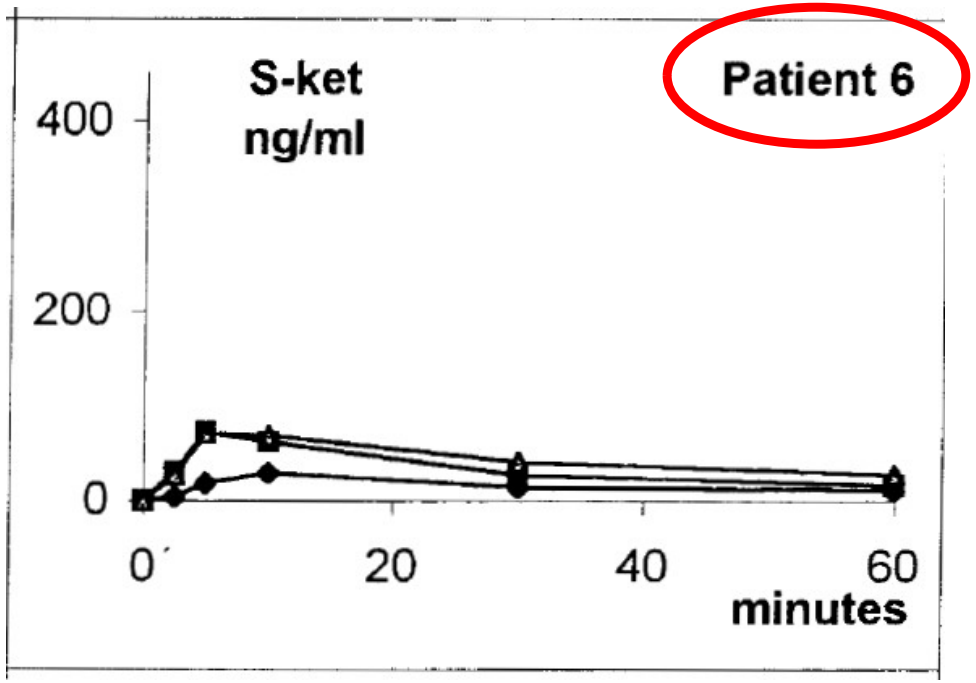

Concentration plasmatique de Kétamine (ng/mL
2000
1800
1600
1400
1200
1000
800
600
400
200
0
2 mg/kg
0,5 mg/kg
0,15 mg/kg
NARCOSE
REVEIL
EFFETS PSYCHO
ANXIETE
ANALGESIE
Nystagmus
Effet anti-hyperalgésique
0
15
30
45
60
75
90
Temps (min)

The analgesic effect of racemic ketamine in patients with chronic ischemic pain due to lower extremity arteriosclerosis obliterans

J. Persson, J. Hasselström, B. Wiklund, A. Heller, J.-O. Svensson and L. L. Gustafsson

Acta Anaesthesiol Scand 1998; **42**: 750–758





Methods: Eight patients with rest pain in the lower extremity due to arteriosclerosis obliterans were given sub-dissociative doses of 0.15, 0.30, or 0.45 mg/kg racemic ketamine and morphine 10 mg as a 5-min infusion on four separate days in a cross-over, double-blind, randomised protocol. Plasma levels of (S)- and (R)-ketamine and their nor-metabolites were analysed with

Pharmacodynamie

2 énantiomères

S(+) vs R(-)

HAUTE AUTORITÉ DE SANTÉ

COMMISSION DE LA TRANSPARENCE

21 JUILLET 2021

eskétamine

ESKETAMINE IDD 5 mg/ ml et 25 mg/ ml, solution injectable pour perfusion

Avis favorable au remboursement dans :

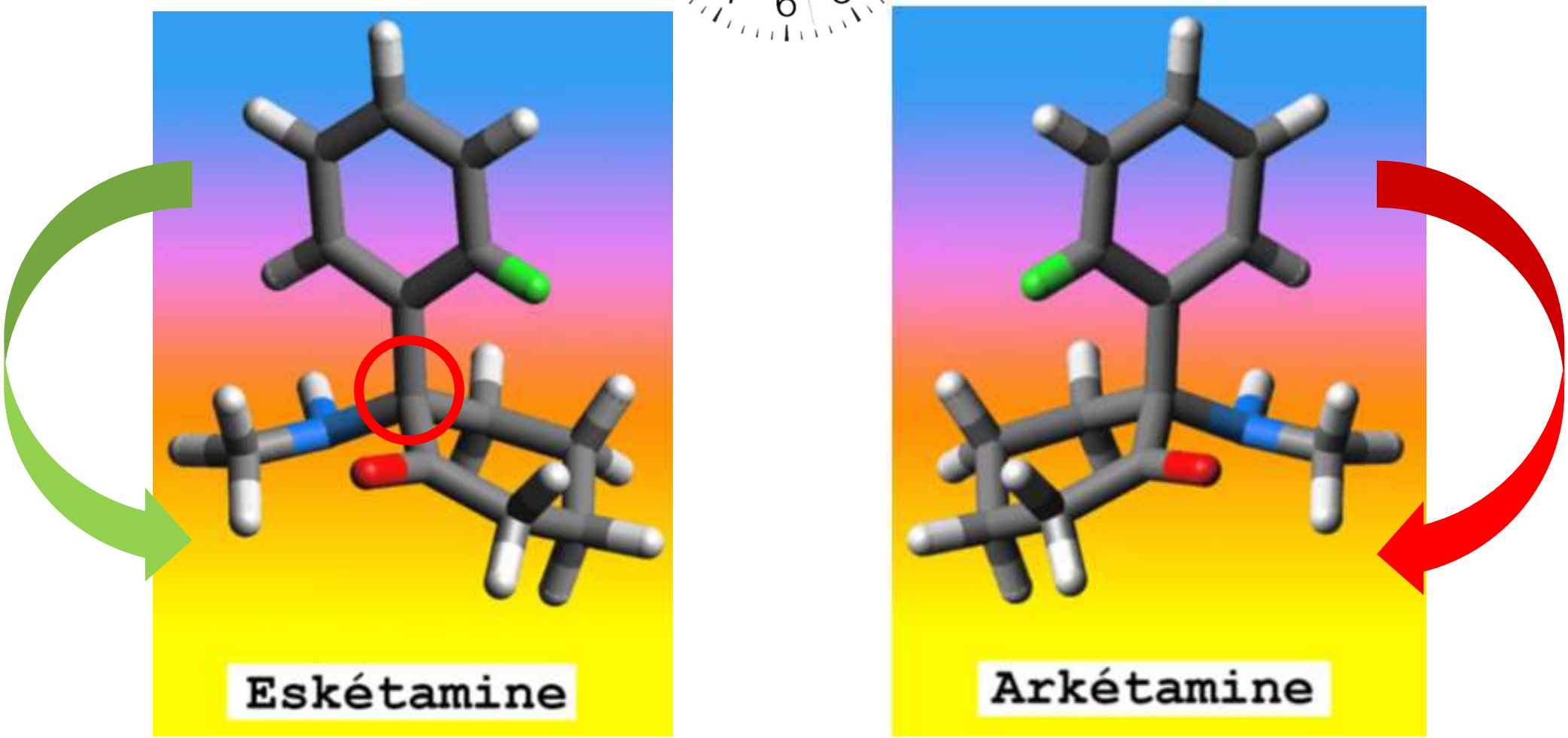
- induction et maintien de l'anesthésie générale, comme seul anesthésique ou en association avec des hypnotiques ;
- anesthésie et soulagement de la douleur (analgésie) en médecine d'urgence ;
- contrôle de la douleur liée à la respiration artificielle (intubation).

Que veut dire

?

S

R



Dextrogyre (+)

Lévogyre (-)

13

Effets hypnotiques et analgésiques

COMPARATIVE PHARMACOLOGY OF THE KETAMINE ISOMERS

Studies in Volunteers

P. F. WHITE, J. SCHÜTTLER, A. SHAFER, D. R. STANSKI, Y. HORAI AND A. J. TREVOR

Br. J. Anaesth. (1985), 57, 197–203

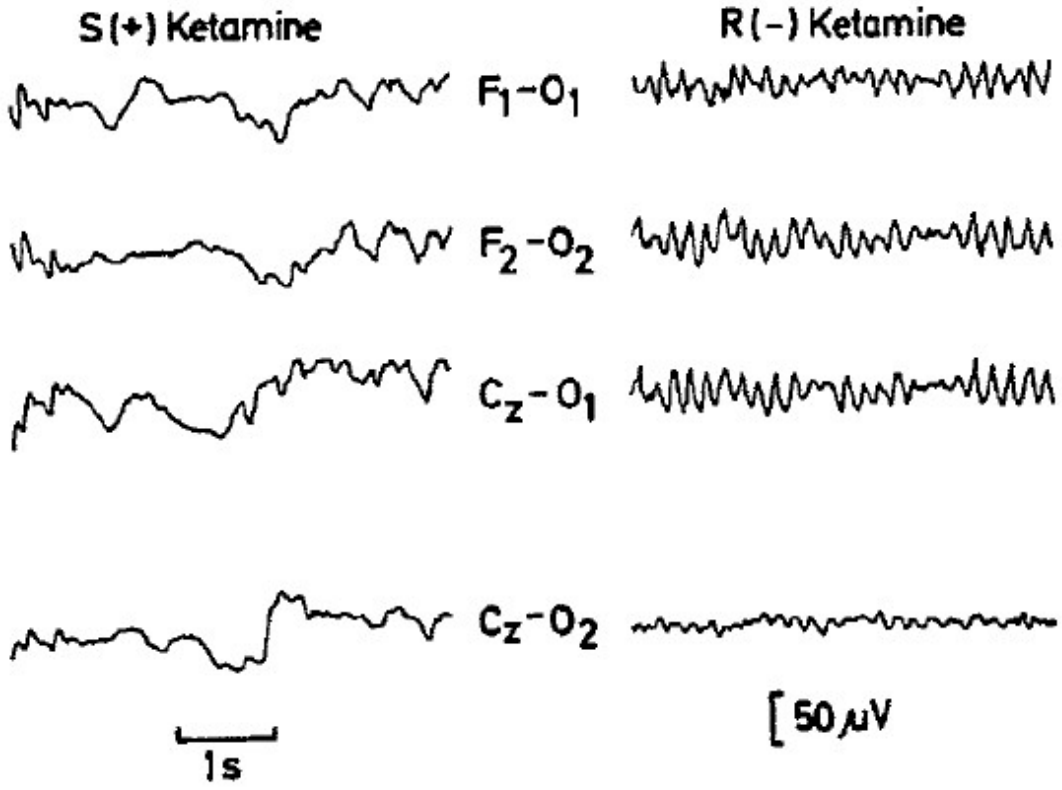


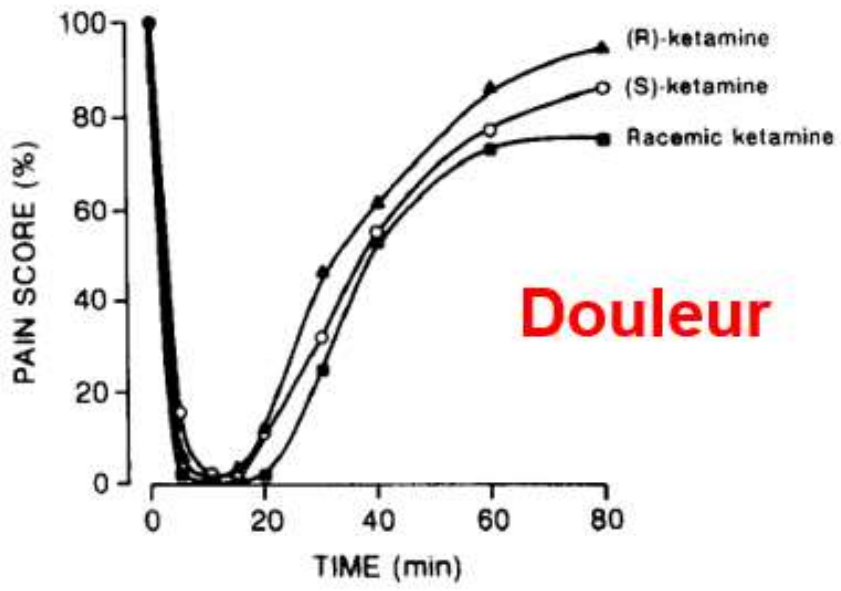
FIG. 2. A typical four-lead EEG pattern demonstrating the *maximal* slowing during or immediately after the infusion of S(+) ketamine or the R(−) isomer i.v.

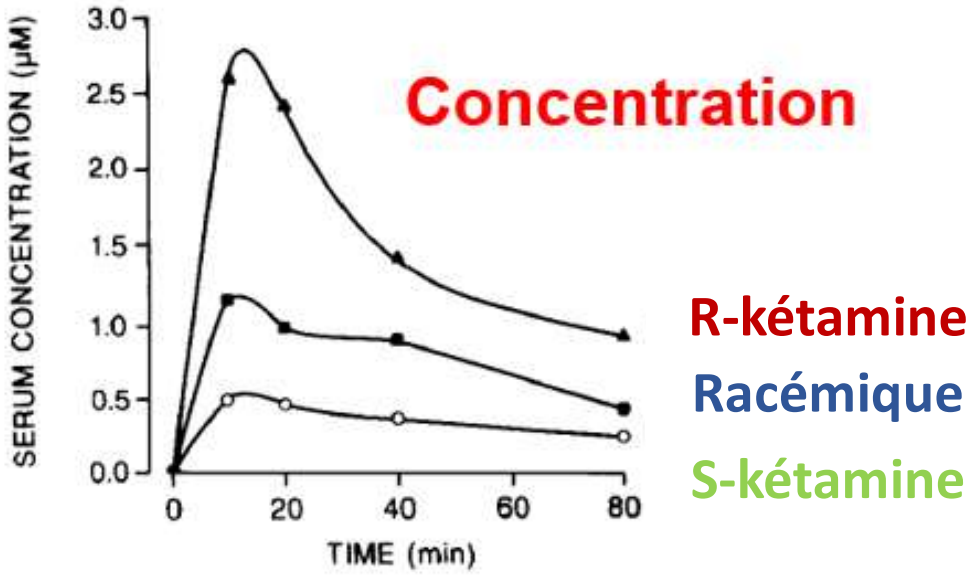
Effect of ketamine, an NMDA receptor inhibitor, in acute and chronic orofacial pain

Lene Cecilie Mathisen [a,1], Per Skjelbred [b], Lasse A. Skoglund [c] and Ivar Øye [a,*]

Pain, 61 (1995) 215–220

The various forms of ketamine were given on an individual basis, either i.m. or intravenously (i.v.) as a single dose sometimes followed by continuous infusion. The patients recorded their pain on the VAS described above and the treatment goal was to obtain analgesia for a time period of at least 15 min. This study was regarded as a pilot investigation. It was not blinded, placebo was not included, and the





Anesthesia with S(+)-ketamine

E. Pfenninger and S. Himmelseher[1]

Universitaetsklinik fuer Anaesthesiologie, Klinikum der Universitaet Ulm, Ulm, Germany; [1]Institut fuer Anaesthesiologie, Klinikum rechts der Isar, Technische Universitaet Muenchen

Introduction

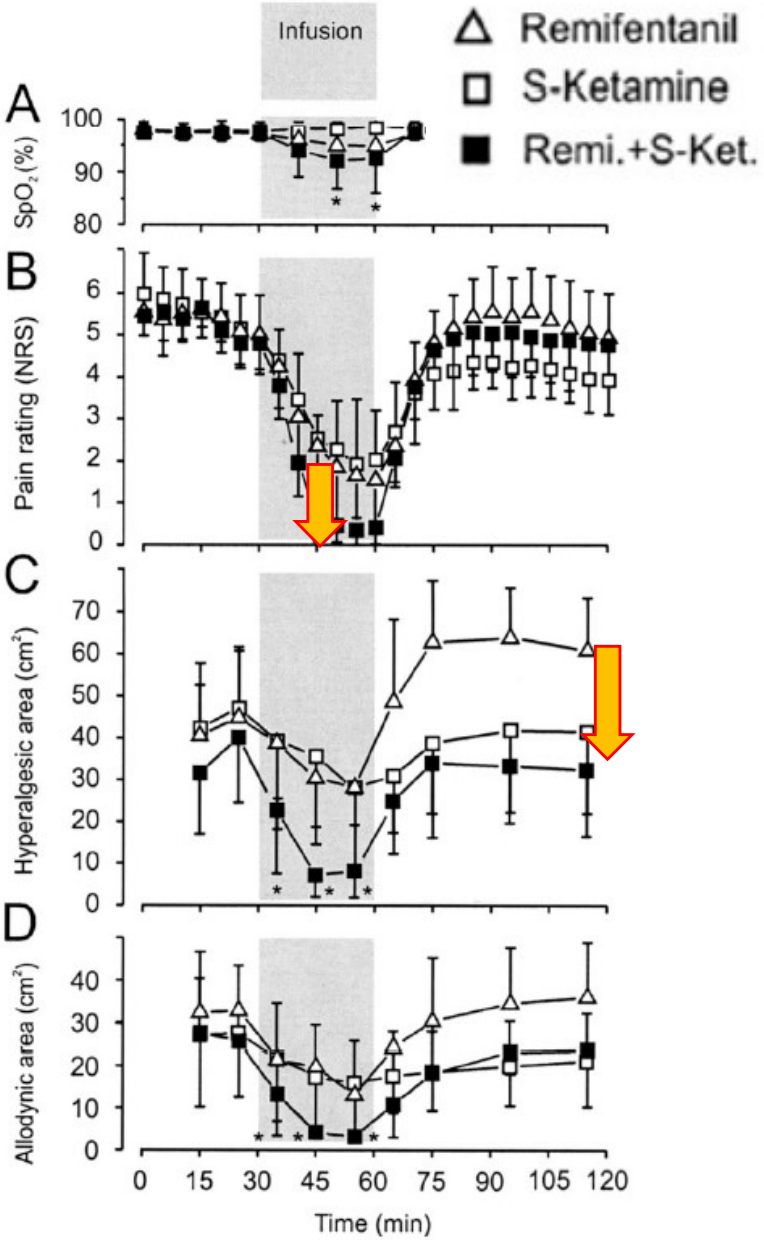
In 1992, the US Food and Drug Administration released a policy statement supporting the study, development and pharmaceutical evaluation of individual enantiomers of racemic mixtures of clinically avaliable drug preparations (1). After selective enantiomeric separation of the anesthetic and analgesic ketamine racemate, the right-handed S(+)-compound may now be clinically used within the group of intravenous anesthetics of the second generation. Many clinical trials have proven that the use of isolated S(+)-ketamine offers the opportunity of administering half the dose of racemic ketamine with the same pharmacologic effects as racemic ketamine. As a consequence, the introduction of S(+)-ketamine into the German commercial market followed in 1997. It should be noted that this is a remarkable success of an academic request for a purified xenobiotic isomer.

1997

Differential Modulation of Remifentanil-induced Analgesia and Postinfusion Hyperalgesia by S-Ketamine and Clonidine in Humans

Wolfgang Koppert, M.D., Reinhard Sittl, M.D.,† Karin Scheuber, M.D.,‡ Monika Alsheimer, M.D.,† Martin Schmelz, M.D.,§ Jürgen Schüttler, M.D.‖*

Anesthesiology 2003; 99:152–9



Methods: **Thirteen volunteers were enrolled in this randomized, double-blind, placebo-controlled study. Transcutaneous electrical stimulation at a high current density (2 Hz, 67.3 ± 16.8 mA, mean ± SD) induced acute pain (numerical 11-point rating scale: 5–6 out of 10) and stable areas of mechanical hyperalgesia to punctate stimuli and touch (allodynia). The magnitude of pain and area of hyperalgesia were assessed before, during, and after drug infusion (remifentanil at 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and *S*-ketamine at 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ over a period of 30 min, respectively; clonidine infusion at 2 $\mu g/kg$ for 5 min).**

Eskétamine + rémifentanil

- **Potentialisation**
- **Diminution de l'hyperalgésie**

Expérience clinique i.v.

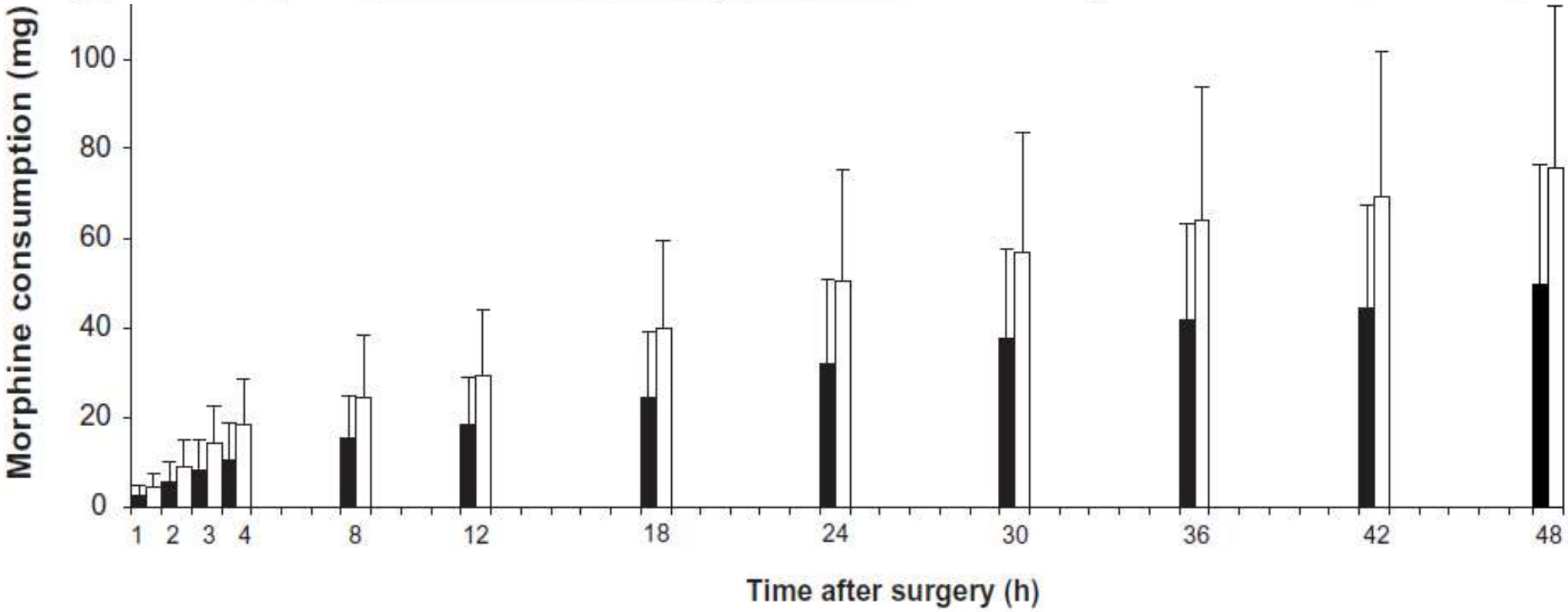
A randomised, controlled study of peri-operative low dose s(+)-ketamine in combination with postoperative patient-controlled s(+)-ketamine and morphine after radical prostatectomy*

Péri opératoire

D. G. Snijdelaar,[1] H. B. Cornelisse,[2] R. L. Schmid[3] and J. Katz[4]

Anaesthesia, 2004, **59**, pages 222–228

In a randomised, double-blind prospective study we compared the effects on postoperative pain and analgesic consumption of intra-operative s(+)-ketamine (100 $\mu g.kg^{-1}$ bolus and a continuous infusion of 2 $\mu g.kg^{-1}.min^{-1}$) followed by postoperative patient-controlled analgesia with morphine (1 mg per bolus) plus s(+)-ketamine (0.5 mg per bolus), or intra-operative saline followed by



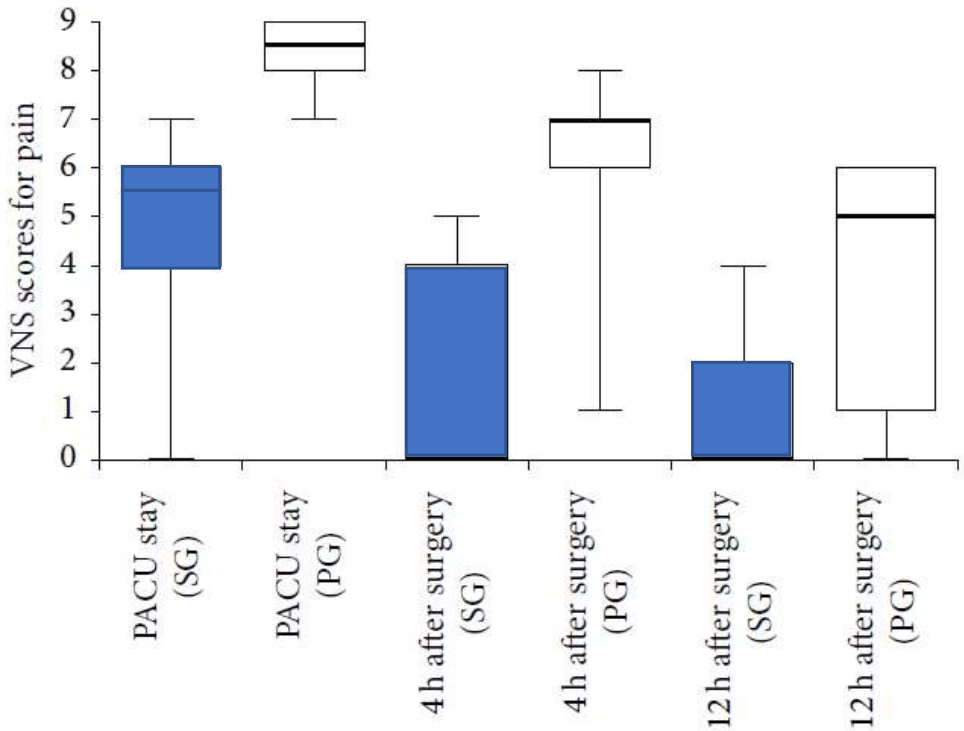
Efficacy of Continuous S(+)-Ketamine Infusion for Postoperative Pain Control: A Randomized Placebo-Controlled Trial

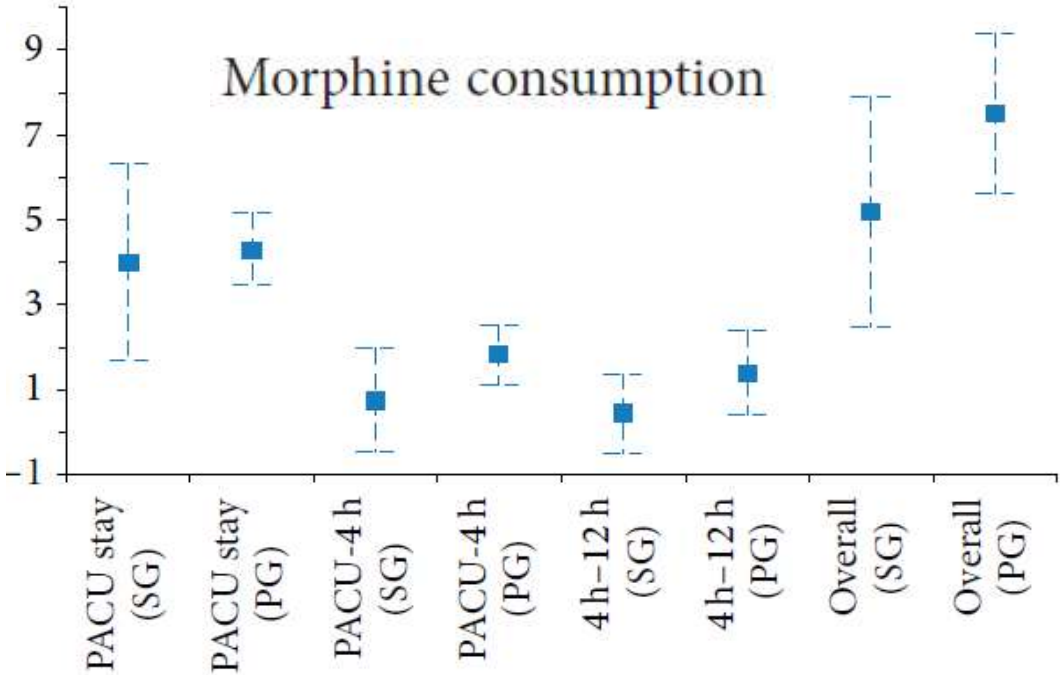
Péri opératoire

Luiz Eduardo de Paula Gomes Miziara,[1] Ricardo Francisco Simoni,[1,2] Luís Otávio Esteves,[1] Luis Henrique Cangiani,[1] Gil Fernando Ribeiro Grillo-Filho,[1] and Anderson Garcia Lima e Paula[1]

Anesthesiology Research and Practice Volume 2016, Article ID 6918327, 6 pages

Aim. A double-blind, randomized, placebo-controlled trial was designed to evaluate the efficacy of continuous intraoperative infusion of S(+)-ketamine under intravenous anesthesia with target-controlled infusion of remifentanil and propofol for postoperative pain control. *Methods.* Forty-eight patients undergoing laparoscopic cholecystectomy were assigned to receive continuous S(+)-ketamine infusion at a rate of 0.3 mg·kg^{-1}·h^{-1} (n = 24, intervention group) or an equivalent volume of saline





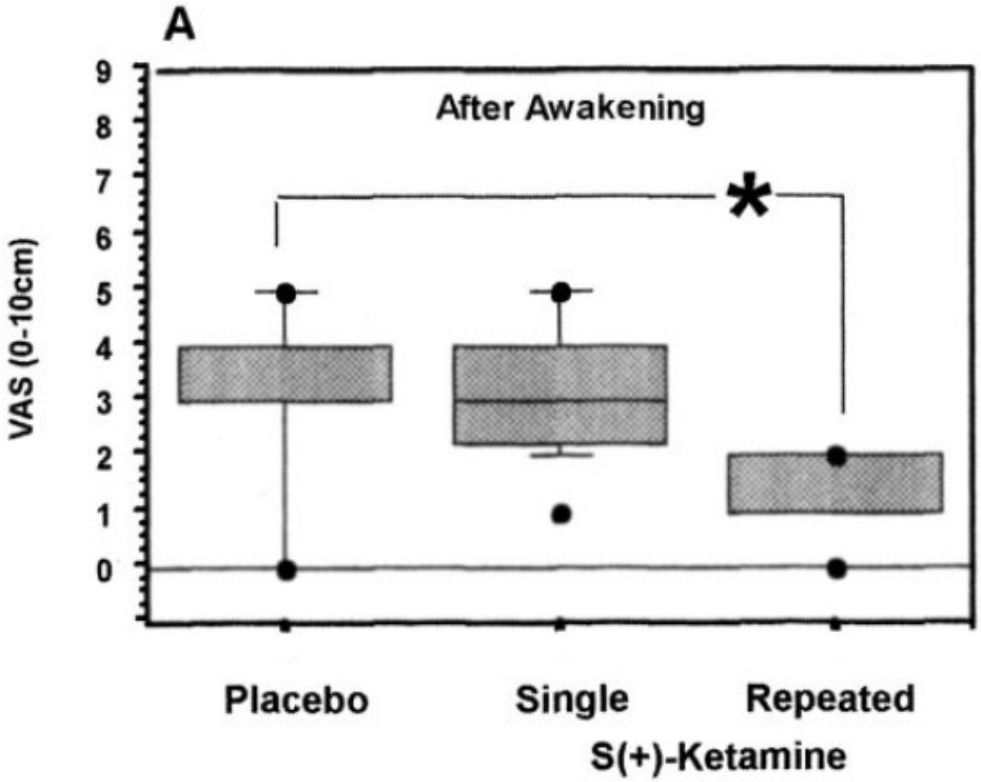
Improvement of Pain Treatment After Major Abdominal Surgery by Intravenous S(+)-Ketamine

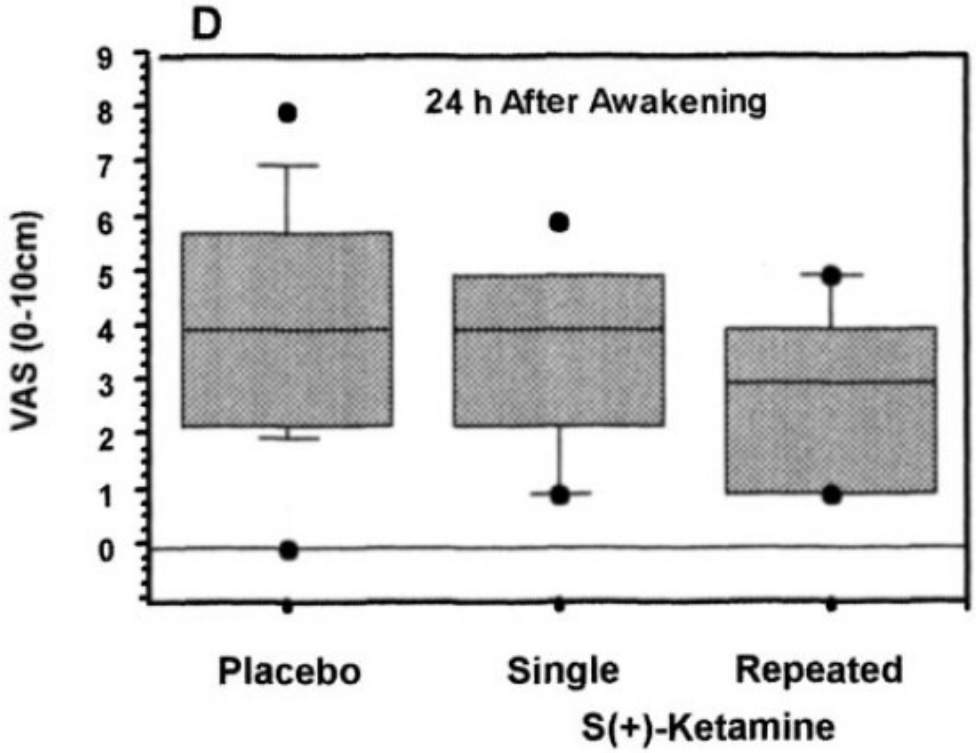
Helena Argiriadou, MD*, Sabine Himmelseher, MD†, Pinelopi Papagiannopoulou, MD‡, Mary Georgiou, MD‡, Fotios Kanakoudis, MD‡, Maria Giala, MD*, and Eberhard Kochs, MD, PhD†

(Anesth Analg 2004;98:1413–8)

stereoisomer of ketamine. Patients were randomized to receive placebo, 0.5 mg/kg preincisional S(+)ketamine, or 0.5 mg/kg preincisional and 0.2 mg/kg intraoperative S(+)-ketamine repeated at 20-min intervals. In the postoperative period, epidural ropivacaine (2 mg/mL; 0.12 mL · kg^{-1} · h^{-1}) was infused for pain therapy. Pa-

Péri opératoire





Intraoperative ketamine reduces immediate postoperative opioid consumption after spinal fusion surgery in chronic pain patients with opioid dependency: a randomized, blinded trial

Rikke Vibeke Nielsen[a,*], Jonna Storm Fomsgaard[a], Hanna Siegel[b], Robertas Martusevicius[a], Lone Nikolajsen[c], Jørgen Berg Dahl[d], Ole Mathiesen[e]

PAIN 158 (2017) 463–470

analogue scale), adverse events, and persistent pain 6 months postoperatively. One hundred fifty patients were randomly assigned to intraoperative S-ketamine bolus 0.5 mg/kg and infusion 0.25 $mg \cdot kg^{-1} \cdot h^{-1}$ or placebo. Postoperatively, patients received their usual opioids, paracetamol and IV patient-controlled analgesia with morphine. In the final analyses, 147 patients were included. Patient-controlled analgesia IV morphine consumption 0 to 24 hours postoperatively was significantly reduced in the ketamine group compared with the placebo group: 79 (47) vs 121 (53) mg IV, mean difference 42 mg (95% confidence interval −59 to −25), $P <$ 0.001. Sedation was significantly reduced in the ketamine group 6 and 24 hours postoperatively. There were no significant differences regarding acute pain, nausea, vomiting, hallucinations, or nightmares. Back pain at 6 months postoperatively compared with preoperative pain was significantly more improved in the ketamine group compared with the placebo group, $P = 0.005$. In conclusion,

Péri opératoire

3.1. Morphine consumption

The total 24-hour PCA morphine consumption was significantly reduced in the ketamine group compared with the placebo group: 79 (47) vs 121 (53) mg IV morphine with a mean difference of 42 mg (95% CI −59 to −25), $P < 0.001$. There was no

A study of low-dose S-ketamine infusion as "preventive" pain treatment for cesarean section with spinal anesthesia: benefits and side effects

E. SUPPA, A. VALENTE, S. CATARCI, B. A. ZANFINI, G. DRAISCI

(Minerva Anestesiol 2012;78:774-81)

S-Ketamine 0.5 mg/kg *i.m.* bolus 10 minutes after birth
2 µg/kg/min *i.v.* continuous infusion for 12 h.

Péri opératoire (per et post opératoire)

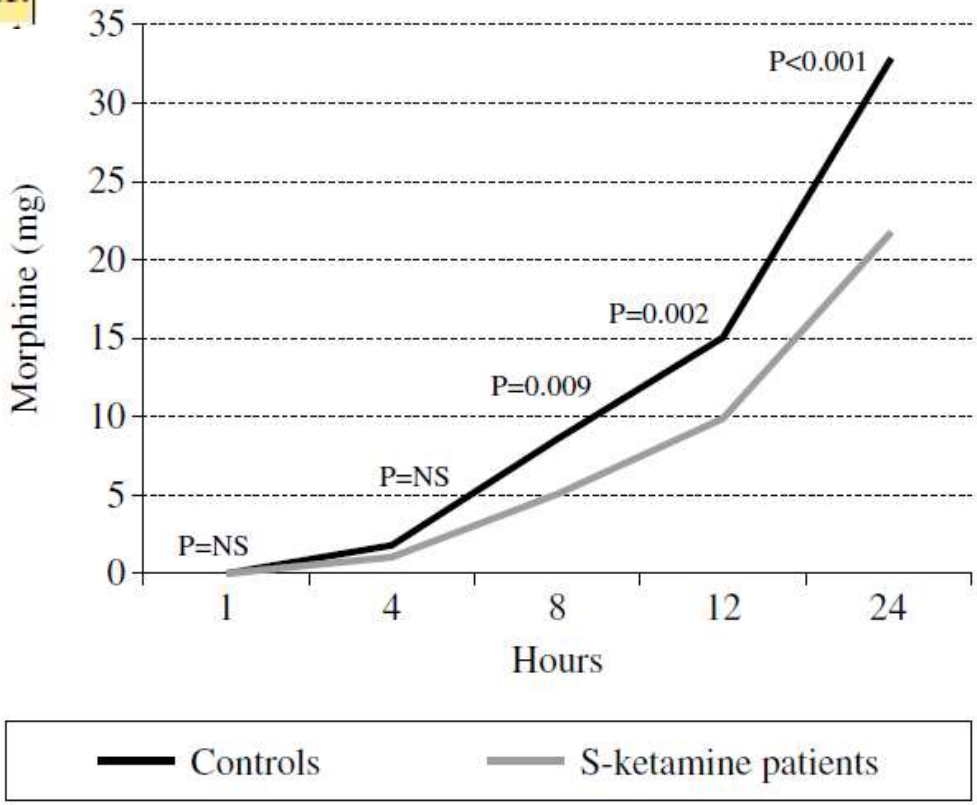


Figure 1.—Morphine consumption.

S-ketamine in patient-controlled analgesia reduces opioid consumption in a dose-dependent manner after major lumbar fusion surgery: A randomized, double-blind, placebo-controlled clinical trial

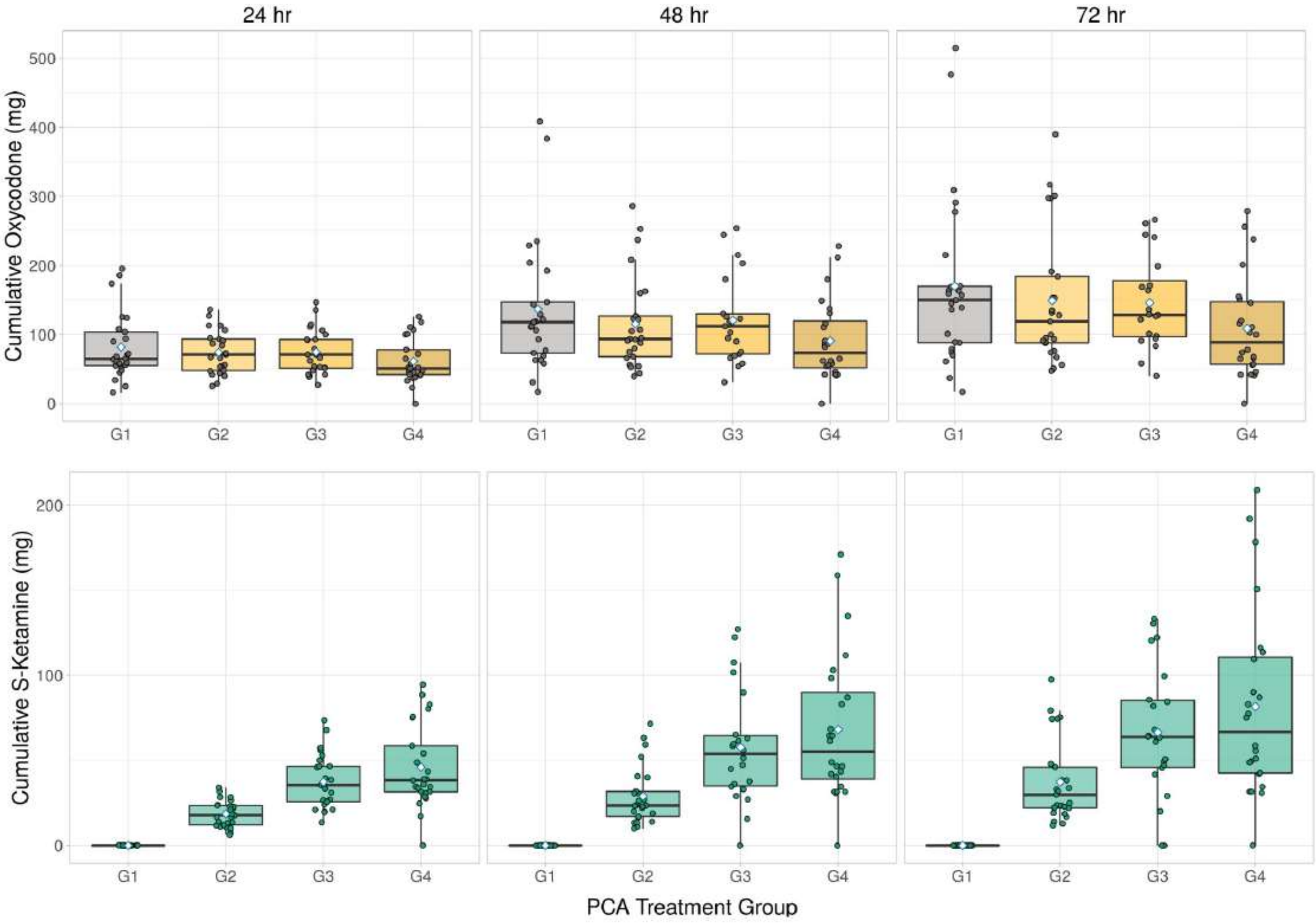
PLOS ONE

June 7, 2021

Post opératoire

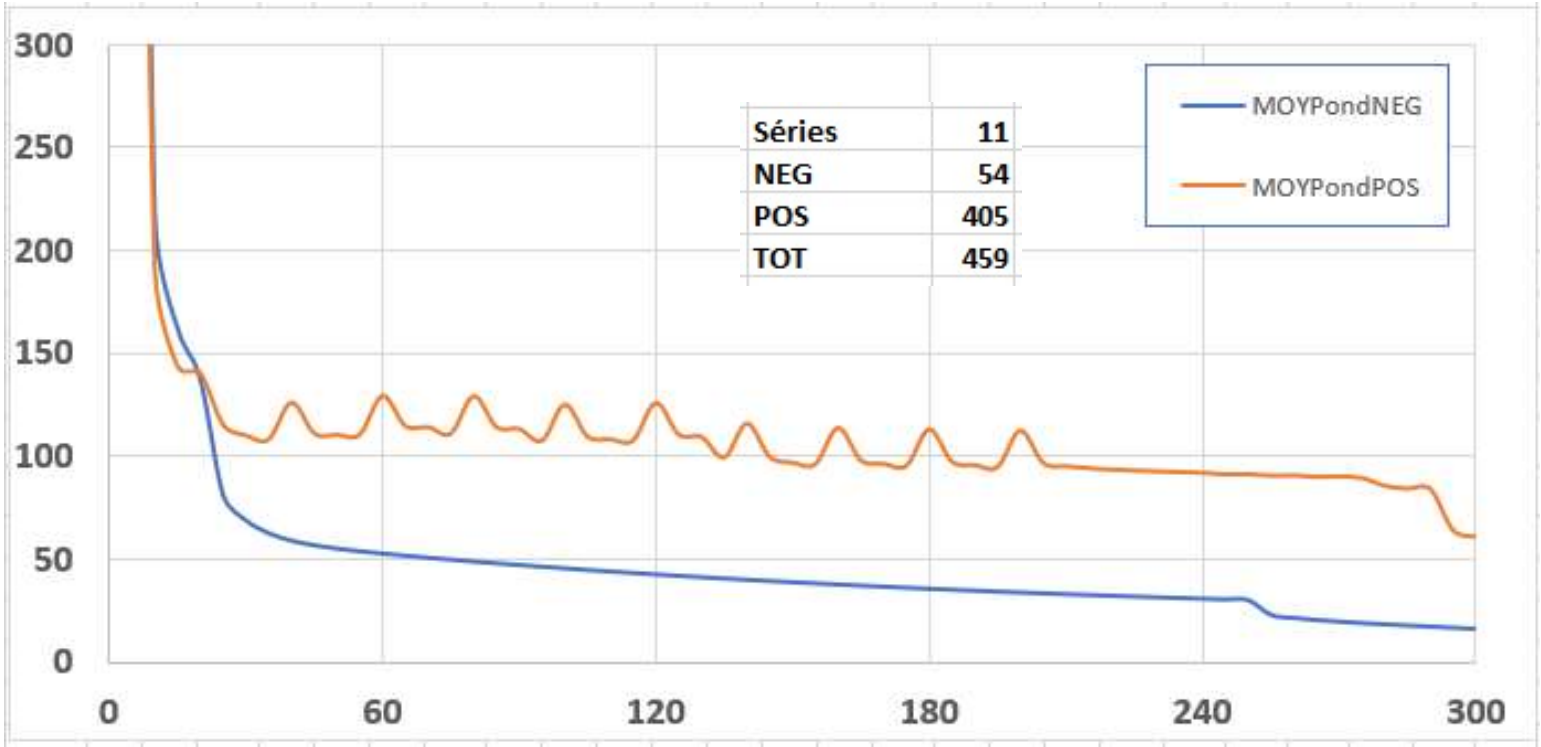
Elina C. V. Brinck[1,2☯¤a], Taru Virtanen[3☯¤b], Sanna Mäkelä[4], Venla Soini[5], Ville-Veikko Hynninen[4], Jukka Mulo[4], Urmas Savolainen[4], Juho Rantakokko[5], Kreu Maisniemi[1], Antti Liukas[3], Klaus T. Olkkola[2], Vesa Kontinen[6], Pekka Tarkkila[1], Marko Peltoniemi[3], Teijo I. Saari[3,4¤b]*

We randomized 107 patients at two tertiary hospitals in a double-blinded, placebo-controlled clinical trial of adults undergoing major lumbar spinal fusion surgery. Patients were randomly allocated to four groups in order to compare the effects of three different doses of adjunct S-ketamine (0.25, 0.5, and 0.75 mg ml-1) or placebo on postoperative analgesia in oxycodone PCA. Study drugs were administered for 24 hours postoperative after which oxycodone-PCA was continued for further 48 hours. Our primary outcome was cumulative oxycodone consumption at 24 hours after surgery.


24 hr
48 hr
72 hr
Cumulative Oxycodone (mg)
500
400
300
200
100
0
G1
G2
G3
G4
Cumulative S-Ketamine (mg)
200
100
0
PCA Treatment Group

Péri opératoire

auteur	Date	Chirurgie	Type	N	K	C	IND	PEROP	POSTOP	J2-J3	Effet
Jaksch	2002	knee ligament repair	RCT	30	15	15	0.5	2 µ	2 µ pdt 2 h	0	NEG
Spreng	2010	haemorrhoidectomy	RCT	77	39	38	0.35	5µ	0	0	NEG
Lahtinen	2004	CABG	RCT	90	44	46	0.075	1.25 µ	1.25 µ	48 h	POS
Snijdelaar	2004	radical prostatectomy	RCT	25	13	12	0.1	2 µ	PCA 0.5 mg	48h	POS
Argiriadou	2004	Abdominal	RCT	45	15	15	0.5	0	0	0	
Argiriadou	2011	thoracotomy	RCT	53	27	26	0.5	0.4	0	0	POS
Mendola	2012	thoracotomy	RCT	62	32	30	0	0.1	0.1	60 h	POS
Bornemann-Cimenti	2016	Abdominal	RCT	56	18	19	0.25	0.125	0.125	48h	POS
Miziara	2016	laparoscopic cholecystectomy	RCT	42	21	21	0	0.3	0	0	POS
Nielsen 2017	2017	spinal fusion	RCT	147	74	73	0.5	0.25	0	0	POS
Brinck	2021	spinal fusion	RCT	189	65	62	0.5	0.12	0	0	POS



Expérience clinique périmédullaire

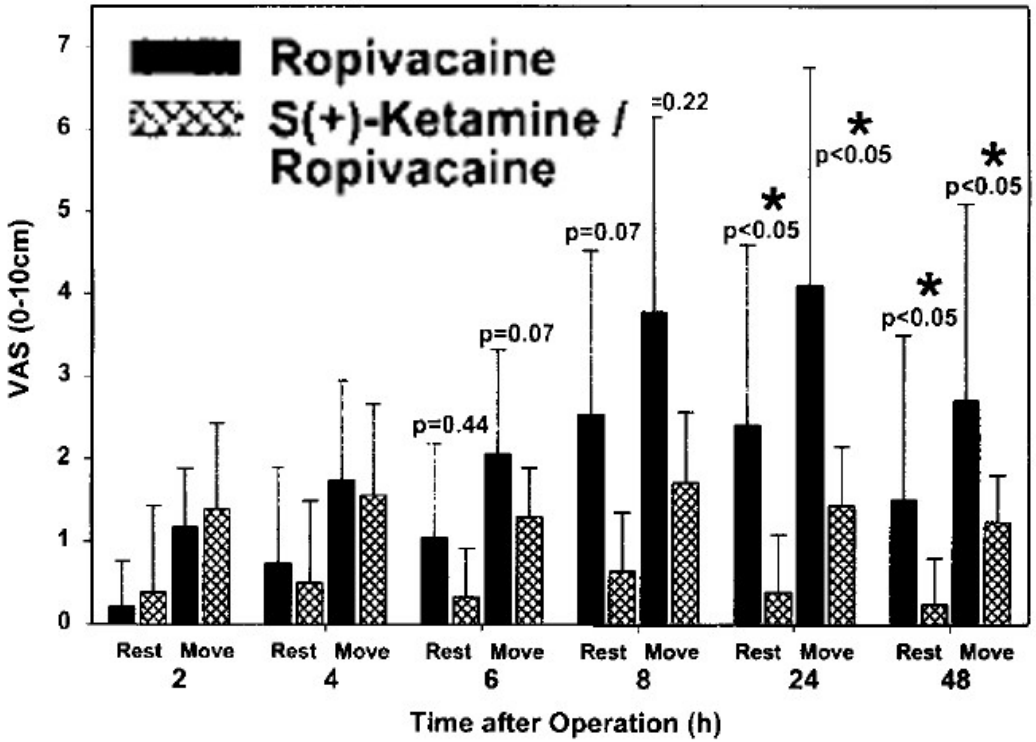
Small-Dose S(+)-Ketamine Reduces Postoperative Pain When Applied with Ropivacaine in Epidural Anesthesia for Total Knee Arthroplasty

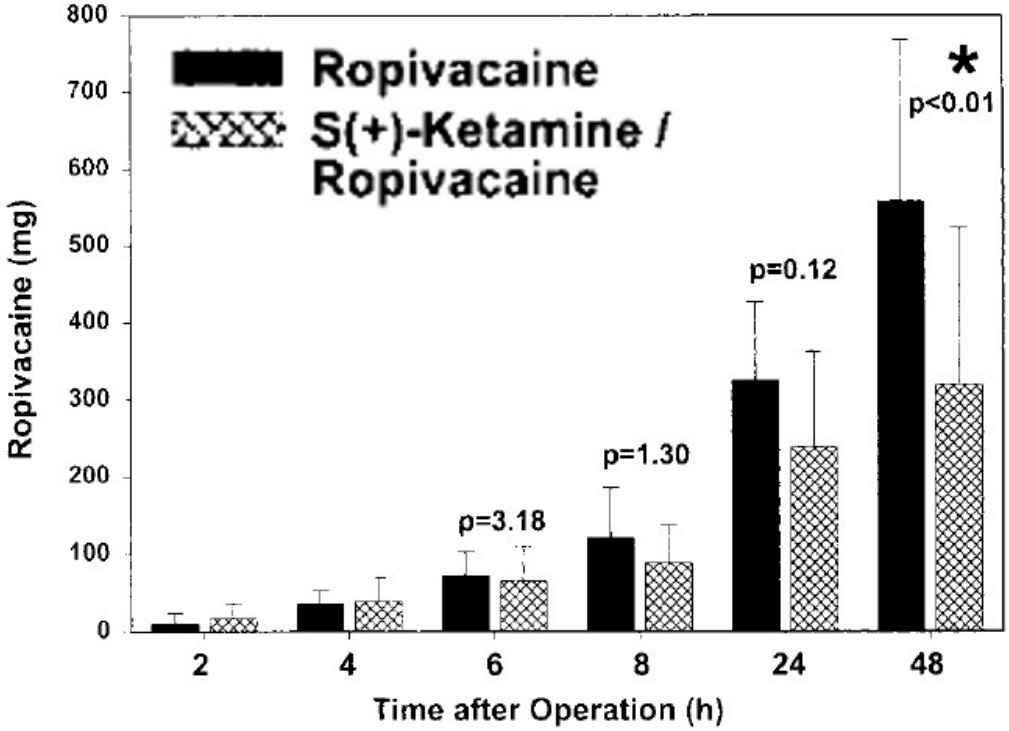
Anesth Analg 2001;92:1290–5

Sabine Himmelseher, MD, Doris Ziegler-Pithamitsis, MD, Helena Argiriadou, MD, Jan Martin, MD, Sabine Jelen-Esselborn, MD, and Eberhard Kochs, MD

Péridural

After lumbar epidural anesthesia with ropivacaine (10 mg/mL, 10–20 mL), 19 patients received 0.9% epidural saline, and 18 patients received 0.25 mg/kg epidural S(+)-ketamine 10 min before surgical incision.





Double-blind randomized controlled trial of caudal *versus* intravenous S(+)-ketamine for supplementation of caudal analgesia in children

Caudale 0,5 mg/kg

S. J. Martindale, P. Dix and P. A. Stoddart*

British Journal of Anaesthesia **92** (3): 344–7 (2004)

Methods. Sixty children undergoing caudal block during general anaesthesia for hernia repair or orchidopexy were prospectively randomized to one of three groups: the bupivicaine group received plain bupivacaine 0.25% 1 ml kg^{-1}; the caudal ketamine group received caudal plain bupivacaine 0.25% 1 ml kg^{-1} with S(+)-ketamine 0.5 mg kg^{-1}; the i.v. ketamine group received caudal plain bupivacaine 0.25% 1 ml kg^{-1} plus S(+)-ketamine 0.5 mg kg^{-1} i.v.. Postoperative measurements included analgesic requirements and modified objective pain score for the first 24 h.

Results. The median time to first analgesia was significantly longer in the caudal ketamine group (10 h) than in the i.v. ketamine (4.63 h) or bupivacaine (4.75 h) groups (P=0.01). Significantly fewer doses of analgesia were required over the first postoperative 24 h by subjects in the caudal ketamine group (median 1) compared with the i.v. ketamine (median 2) or bupivacaine (median 2.5) groups (P<0.05). There was no difference between the groups in the incidence of postoperative nausea and vomiting or psychomotor reactions.

Conclusions. We have demonstrated that the addition of caudal S(+)-ketamine to bupivacaine prolongs the duration of postoperative analgesia. However, the same dose of i.v. S(+)-ketamine combined with a plain bupivacaine caudal provides no better analgesia than caudal bupivacaine alone, indicating that the principal analgesic effect of caudal S(+)-ketamine results from a local neuroaxial rather than a systemic effect.

Comparing caudal and intravenous ketamine for supplementation of analgesia after Salter innominate osteotomy

Hamid Reza Amiri · Ramin Espandar · Mehdi Sanatkar

J Child Orthop (2012) 6:479–483

Caudale 1 mg/kg

Methods After the induction of general anesthesia, 36 patients, aged 18 months to 10 years, assigned to undergo orthopedic surgery, received a caudal injection of bupivacaine and were randomly blinded into two groups: one group received 1 mg/kg *S*(+)-ketamine as the caudal group and the other group received 1 mg/kg *S*(+)-ketamine as the intravascular group. Postsurgical measurements included the effectiveness of postsurgical analgesia, which was assessed by using the observational pain scale (OPS),

Group	Caudal group	IV group	*P*-value
Average mean arterial blood pressure (mmHg)	68 ± 12	69 ± 18	0.44
Mean heart rate	95 ± 28	97 ± 24	0.62
Mean duration of analgesic effect (h)	13.35 ± 1.2	9.93 ± 1.6	<0.01
Asked for additional analgesic drugs	8 (44.4 %)	12 (66.6 %)	0.01
Time to first micturation (h)	3.4 (2.8–5.5)	3.2 (2.5–5)	0.84
Time to spontaneous leg movement (h)	2.1 (0.5–4)	2 (0.6–4.5)	0.60
Nausea and vomiting	1	2	0.44
Adverse psychological effects	0	0	–
Respiratory depression	0	0	–

Perioperative intravenous S-ketamine for acute postoperative pain in adults: A systematic review and meta-analysis

Xuemei Wang, Cheng Lin, Lifang Lan, Jingchen Liu*

Journal of Clinical Anesthesia 68 (2021) 110071

Main results: A total of 12 studies were included. The types of surgery included abdominal surgery, thoracotomy, gynecologic surgery, arthroscopic anterior cruciate ligament repair, cardiac surgery, laparoscopic cholecystectomy, lumbar spinal fusion surgery, radical prostatectomy, and hemorrhoidectomy. There were significant improvements in resting pain scores at 4, 12 and 24 h with S-ketamine versus placebo [4 h: standardized mean difference (SMD) -1.11; 95% confidence interval (CI): −1.53, −0.68, $p < 0.00001$; GRADE = moderate; 12 h: SMD −0.88; 95%CI: −1.42, −0.34, $p = 0.001$; GRADE = moderate; 24 h: SMD -0.39; 95%CI: −0.73, −0.06, $p = 0.02$; GRADE = moderate]. The incidence of pain scores at 48 h showed no statistical difference between the two groups (SMD -0.27; 95%CI: −1.12, 0.58, $p = 0.53$, GRADE = moderate). The movement pain scores were not significantly different between the two groups at each time point (4 h: SMD −0.34; 95%CI: −0.73, 0.05, $p = 0.09$, GRADE = moderate; 12 h: SMD −0.42; 95%CI: −1.46, 0.63, $p = 0.44$, GRADE = low; 24 h: SMD −0.58; 95%CI: −1.25, 0.09, $p = 0.09$, GRADE = moderate; 48 h: SMD −0.49; 95%CI: −1.11, 0.14, $p = 0.13$, GRADE = low). At 4 and 12 h after surgery, the consumption of morphine was significantly reduced in the S-ketamine group (4 h: SMD −0.98; 95%CI: −1.37, −0.06, $p < 0.00001$, GRADE = moderate; 12 h: SMD −1.36; 95%CI: −2.26, −0.46, $p = 0.003$, GRADE = low). There were no significant differences in morphine use at 24 and 48 h between the two groups (24 h: SMD −0.70; 95%CI: −1.42, 0.02, $p = 0.06$, GRADE = low; 48 h: SMD −0.79; 95%CI: −2.26, 1.03, $p = 0.39$, GRADE = low). The risk for nausea [relative risk (RR) = 1.04; 95%CI: 0.83, 1.30, $p = 0.73$], vomiting (RR = 1.07; 95%CI: 0.84, 1.38, $p = 0.57$), and psychotomimetic adverse events (RR = 1.57; 95%CI: 0.82, 2.99, $p = 0.17$) showed no significant increase in the S-ketamine group.

No « magic bullet »

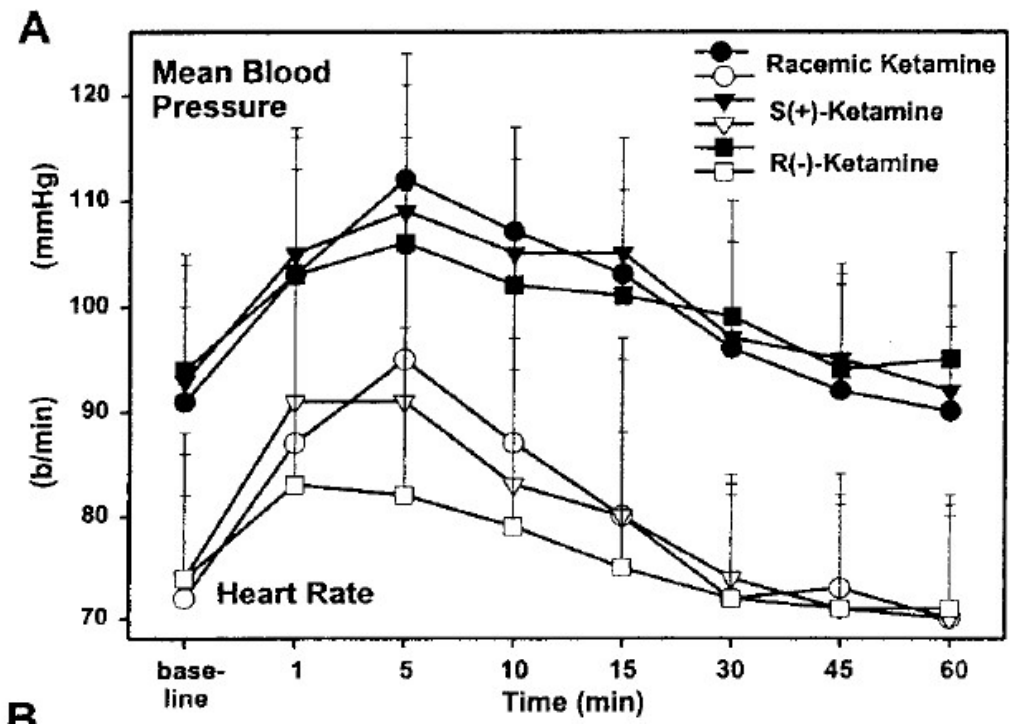
Effets cardiovasculaires

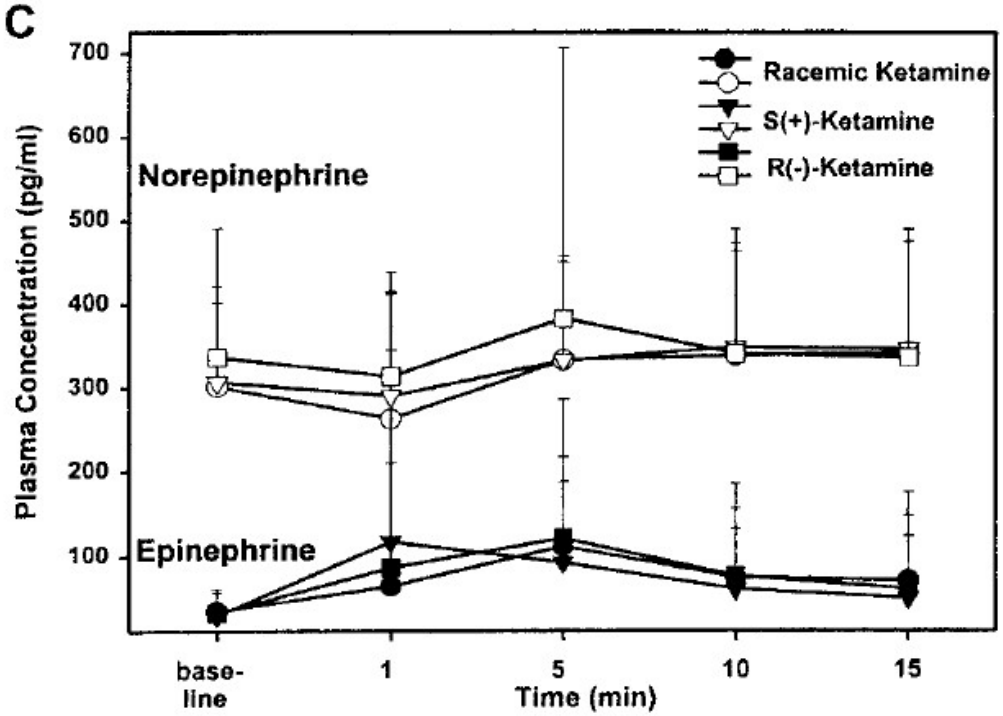
Cognitive Impairment after Small-dose Ketamine Isomers in Comparison to Equianalgesic Racemic Ketamine in Human Volunteers

Ernst G. Pfenninger, M.D., Marcel E. Durieux, M.D., Ph.D.,† Sabine Himmelseher, M.D.‡*

Anesthesiology 2002; 96:357–66

Methods: **Twenty-four subjects received intravenous 0.5 mg/kg racemic, 0.25 mg/kg *S*(+)-, and 1.0 mg/kg *R*(−)-ketamine in a prospective, randomized, double-blind, crossover study. Hemo-**

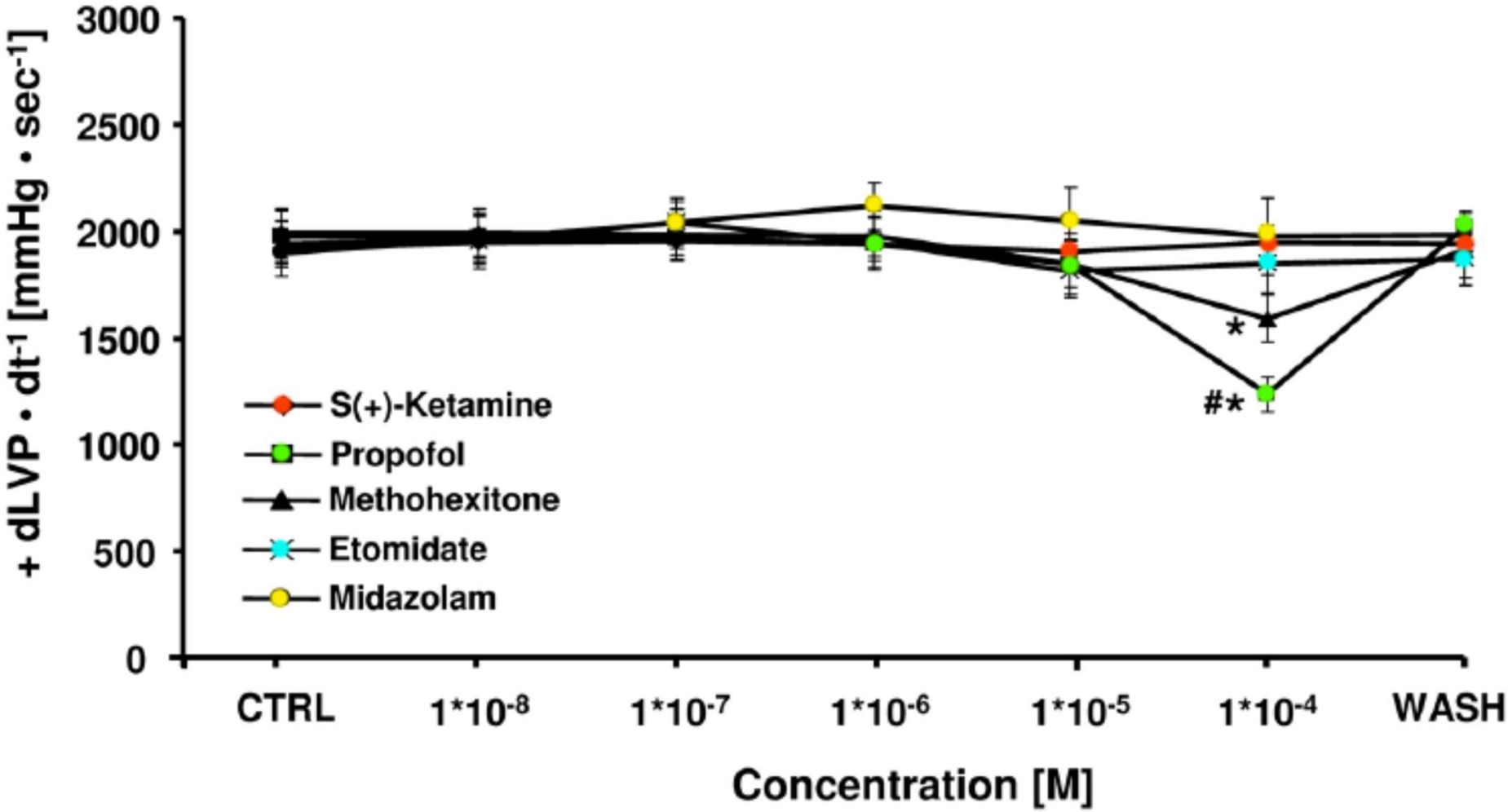




Cardiac effects of induction agents in the septic rat heart

York A Zausig, Hendrik Busse, Dirk Lunz, Barbara Sinner, Wolfgang Zink and Bernhard M Graf

Critical Care 2009, **13**:R144



All drugs except for s(+)ketamine and midazolam decreased contractility.

Actions of Ketamine and Its Isomers on Contractility and Calcium Transients in Human Myocardium

Gudrun Kunst, M.D., Eike Martin, M.D.,† Bernhard M. Graf, M.D.,‡ Siegfried Hagl, M.D.,§ Christian F. Vahl, M.D.‖*

Anesthesiology 1999; 90:1363–71

Results: **Compared with the initial control maximal isometric developed force, maximal isotonic shortening amplitude, contractility, and relaxation increased by 12.5–22.4% after perfusion with S(+)-ketamine at the concentration of 73 μM ($P < 0.05$). In contrast, no changes were seen after addition of 73 μM R(−)-ketamine. The effect of racemic ketamine (73 μM) was between that of the two isomers. At the highest concentration (730 μM) ketamine and its isomers decreased maximal isometric developed force, maximal shortening amplitude, contractility, and relaxation by 26.8–57.4% ($P < 0.05$), accompanied by a significant decrease of the intracellular calcium transient (by 21.0–32.2%, $P < 0.05$).**

Conclusions: **In contrast to R(−)-ketamine, S(+)-ketamine increased isometric force, isotonic shortening, contractility, and relaxation at low concentrations (73 μM) compared with the initial control. At higher concentrations (730 μM) a direct negative inotropic action was observed after perfusion with ketamine and its isomers, which was accompanied by a decreased intracellular Ca^{2+} transient. (Key words: Force; intravenous anesthetics; stereoisomers.)**

Ketamine Stereoselectively Affects Vasorelaxation Mediated by ATP-sensitive K^+ Channels in the Rat Aorta

Mayuko Dojo, M.D., Hiroyuki Kinoshita, M.D.,† Hiroshi Iranami, M.D.,‡ Katsutoshi Nakahata, M.D.,§ Yoshiki Kimoto, M.D.,§ Yoshio Hatano, M.D.‖*

Anesthesiology 2002; 97:882–6

Methods: **Rings of the rat aorta with or without endothelium were suspended for isometric force recording. During contraction to phenylephrine (3×10^{-7} M), vasorelaxation in response to an ATP-sensitive K^+ channel opener levcromakalim (10^{-8} to 10^{-5} M) or a nitric oxide donor sodium nitroprusside (10^{-10} to 10^{-5} M) was obtained. Glibenclamide (10^{-5} M), S(+) ketamine (10^{-4} M), or ketamine racemate (10^{-5} to 10^{-4} M) was applied 15 min before addition of phenylephrine.**

Conclusion: **In the isolated rat aorta, clinically relevant concentrations of ketamine racemate can inhibit relaxation induced by an ATP-sensitive K^+ channel opener, whereas S(+) ketamine did not produce any inhibitory effect on this vasorelaxation. These results suggest that ketamine stereoselectively alters vasodilation *via* ATP-sensitive K^+ channels in the conduit artery.**

Effects of Ketamine and Its Isomers on Ischemic Preconditioning in the Isolated Rat Heart

Andrei Molojavyi, M.D., Benedikt Preckel, M.D., D.E.A.A.,† Thomas Comfère,‡ Jost Müllenheim, M.D.,† Volker Thämer, M.D., Ph.D.,§ Wolfgang Schlack, M.D., Ph.D., D.E.A.A.‖*

Anesthesiology 2001; 94:623

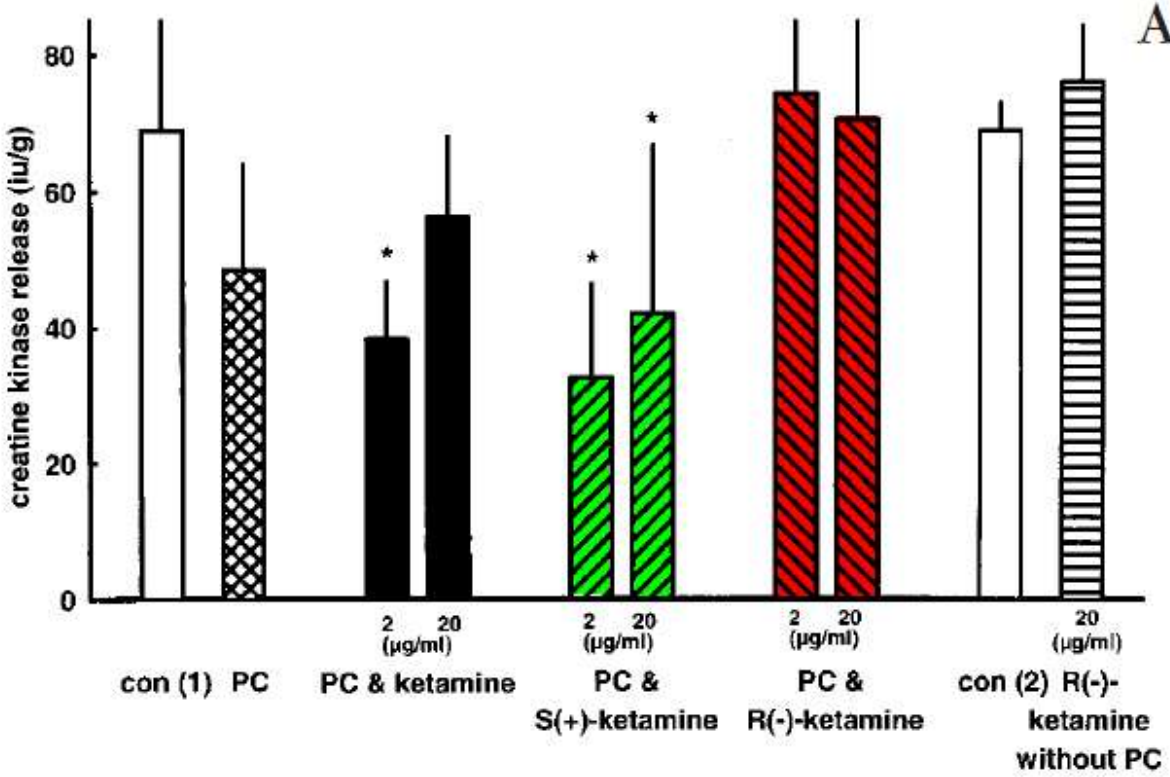


Fig. 3. Cumulative creatine kinase release during reperfusion as a variable of cellular damage. Data are mean values and standard deviation, n = 8; *$P < 0.05$ *versus* control group; PC = ischemic preconditioning.

± 8, 30 ± 14, 41 ± 25 IU/g). After administration of 20 µg/ml ketamine and 2 or 20 µg/ml *R*(−)-ketamine, the protective effects of preconditioning were abolished (LV developed pres-

Comparison of S-(+)-ketamine- with sufentanil-based anaesthesia for elective coronary artery bypass graft surgery: effect on troponin T levels

C. Neuhäuser, V. Preiss, M.-K. Feurer, M. Müller, S. Scholz, M. Kwapisz, M. Mogk and I. D. Welters*

British Journal of Anaesthesia **100 (6):** 765–71 (2008)

Methods. Two hundred and nine patients undergoing elective CABG were randomized to receive either i.v. anaesthesia with sufentanil–midazolam–propofol (SMP; n=108) or S-(+)-ketamine–midazolam–propofol (KMP; n=101). Haemodynamic variables were maintained within the normal range. Invasive haemodynamic monitoring was performed using a pulmonary artery catheter. Plasma cTnT levels were sampled before induction and 1, 6, and 24 h after aortic unclamping. Cardiovascular adverse events, such as electrocardiographic signs of ischaemia, perioperative myocardial infarction, and death, were recorded.

Results. Patient characteristics, cardiac profile, intraoperative management, and the incidence of cardiovascular adverse events were comparable between the groups. Plasma cTnT levels increased after operation in both groups. cTnT levels were significantly lower in the KMP group 6 h after aortic unclamping compared with the SMP group (P=0.004), but did not differ 24 h after aortic unclamping [median (range): SMP 0.4 (0.01–3.9) *vs* KMP 0.4 (0.07–6.6) μg litre^{-1}, P=0.338].

Conclusions. S-(+)-ketamine does not accentuate postoperative cTNT rises in haemodynamically stable elective CABG patients.

Effets
Anti-proinflammatoires

Topical ketamine inhibits albumin extravasation in chemical peritonitis in rats

Acta Anaesthesiol Scand 1995: 39: 174–178

K. Hirota, E. K. Zsigmond, A. Matsuki and S. F. Rabito

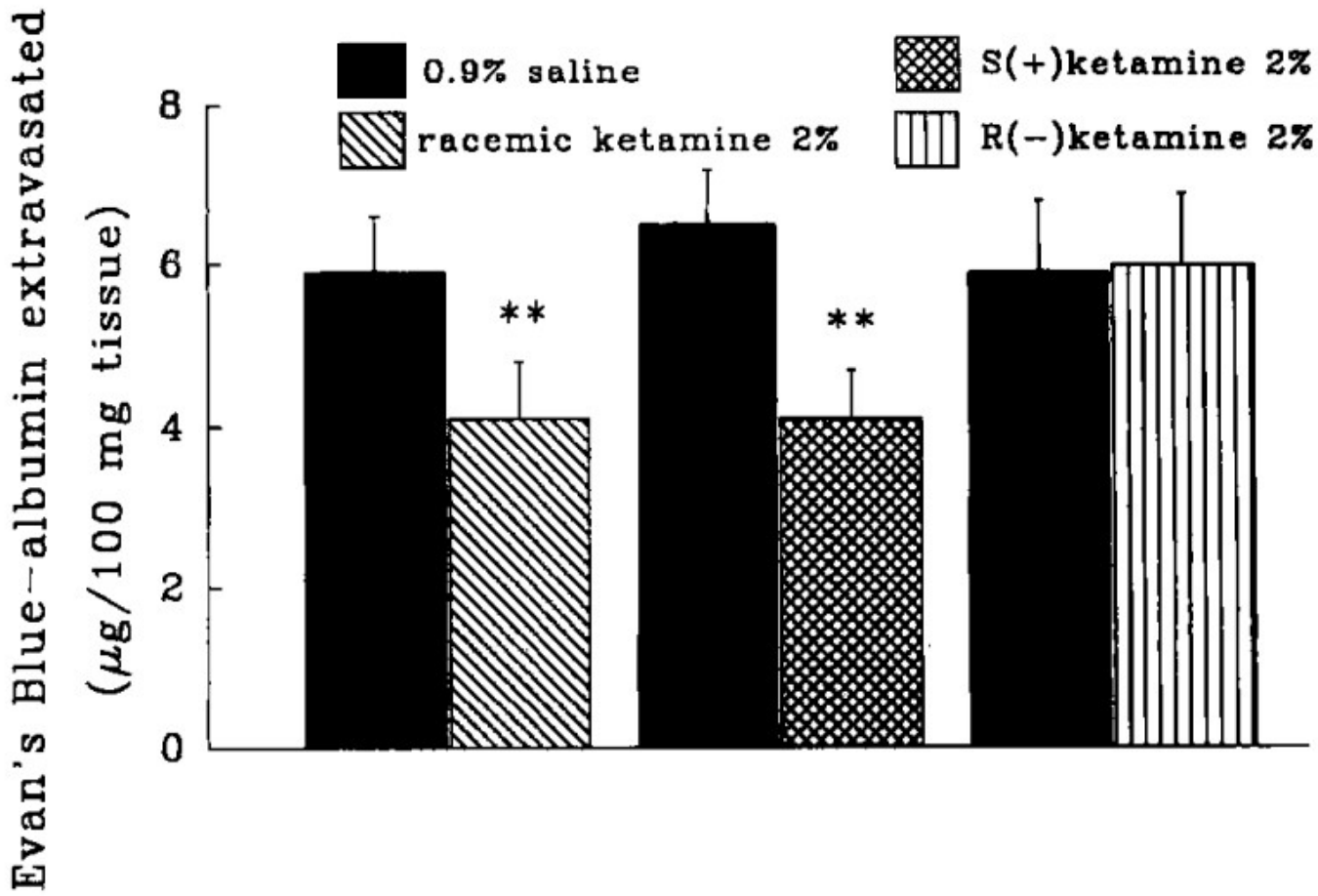


Fig. 3. Effect of racemic ketamine and its isomers S(+)ketamine and R(−)ketamine on Evan's Blue-albumin extravasation in response to chemical peritonitis in rats. Racemic ketamine and its isomers were applied after the colonic surface was exposed to HCl. $^{**}P<0.01$.

S(+)-Ketamine, but Not R(−)-Ketamine, Reduces Postischemic Adherence of Neutrophils in the Coronary System of Isolated Guinea Pig Hearts

Andrea Szekely, MD*, Bernhard Heindl, MD†, Stefan Zahler, PhD†, Peter F. Conzen, MD*, and Bernhard F. Becker, MD, PhD†

(Anesth Analg 1999;88:1017–24)

mers. Seventy-six guinea pig hearts were perfused in the "Langendorff" mode under conditions of constant flow (5 mL/min) using modified Krebs-Henseleit buffer. After 15 min of global warm ischemia, freshly isolated human PMN (10^6) were infused as a bolus into the coronary system during the second minute of reperfusion. PMN adhesion was expressed as the numeric difference between PMN recovered in the effluent and those applied. Series A hearts received 5 μM S(+), 5 μM R(−), or 10 μM racemic ketamine starting 20 min before ischemia and during reperfusion. In Series B hearts, 10 μM nitro-L-arginine, an inhibitor of NO synthase, was added to the perfusate. In Series C, PMN were preincubated for 15 min with 5 μM S(+)- or R(−)-ketamine. Coronary vascular leak was assessed by mea-

isomers: S(+)-ketamine inhibited PMN adherence, R(−)-ketamine worsened coronary vascular leak in

Continuous *S*-(+)-ketamine administration during elective coronary artery bypass graft surgery attenuates pro-inflammatory cytokine response during and after cardiopulmonary bypass

I. D. Welters [1,2], M.-K. Feurer [1], V. Preiss [1], M. Müller [1], S. Scholz [1,3], M. Kwapisz [1], M. Mogk [4] and C. Neuhäuser [1,5*]

British Journal of Anaesthesia **106** (2): 172–9 (2011)

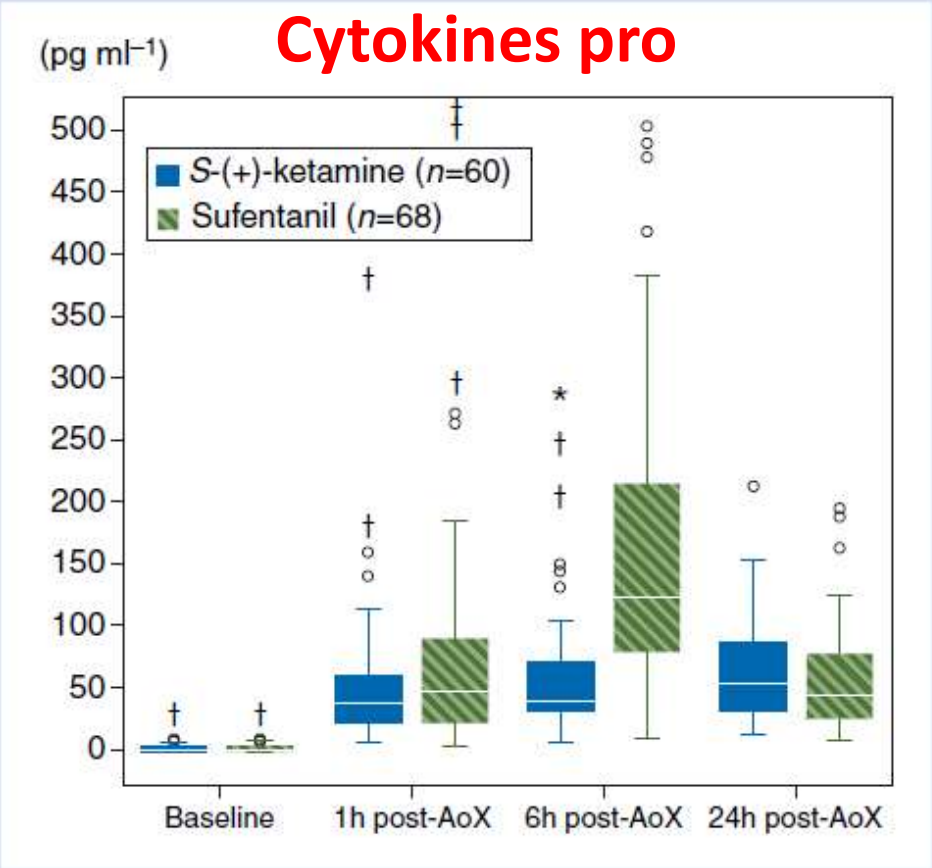


Fig 2 IL-6 plasma levels are presented as box plots for each group and time point. †Outliers from the data set; *significant difference between the groups ($P<0.05$). AoX, aortic cross-clamp.

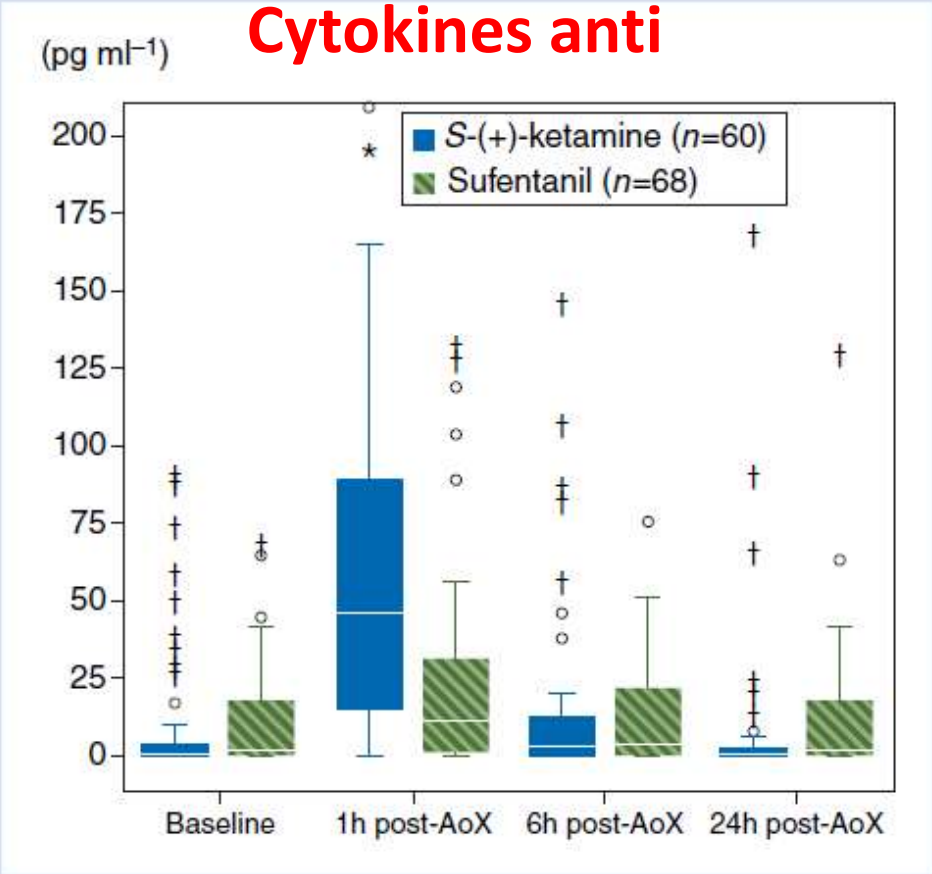


Fig 4 IL-10 plasma levels are presented as box plots for each group and time point. †Outliers from the data set; *significant difference between the groups ($P<0.05$). AoX, aortic cross-clamp.

Effets Cérébraux

S(+)-ketamine

Wien Klin Wochenschr (2018) 130:356–366

Current trends in emergency and intensive care medicine

Helmut Trimmel · Raimund Helbok · Thomas Staudinger · Wolfgang Jaksch · Brigitte Messerer · Herbert Schöchl · Rudolf Likar

Analgesia	In trauma patients fractures, burns, soft tissue trauma, etc.
Analgosedation	During extrication from vehicles, invasive measures in uncooperative patients
Anesthesia	In hypovolemic status and cardiogenic shock
Asthma	Induction of anesthesia in asthmatic status, additive to analgosedation in patients with bronchospasm
Disasters	Proven worldwide as analgesic and anesthetic in mass casualties, disaster relief and war surgery

Table 5 Typical indications for S(+)-ketamine in emergency medicine

Severe brain trauma

S(+)-ketamine is a suitable and safe substance in patients with brain injuries if ventilation and oxygenation are sufficient, even in the hands of less experienced emergency physicians. Contrary to earlier assumptions, therapy with S(+)-ketamine with controlled ventilation does not raise intracranial pressure [36]. As described, due to the blockade of the NDMA receptor, not only an anti-nociceptive effect but also a neuroprotective effect is achieved.

Revising a Dogma: Ketamine for Patients with Neurological Injury?

Sabine Himmelseher, MD*, and Marcel E. Durieux, MD, PhD†

(Anesth Analg 2005;101:524–34)

The Effects of Ketamine-Isomers on Neuronal Injury and Regeneration in Rat Hippocampal Neurons

Sabine Himmelseher, MD, Ernst Pfenninger, MD, and Michael Georgieff, MD

(Anesth Analg 1996;83:505–12)

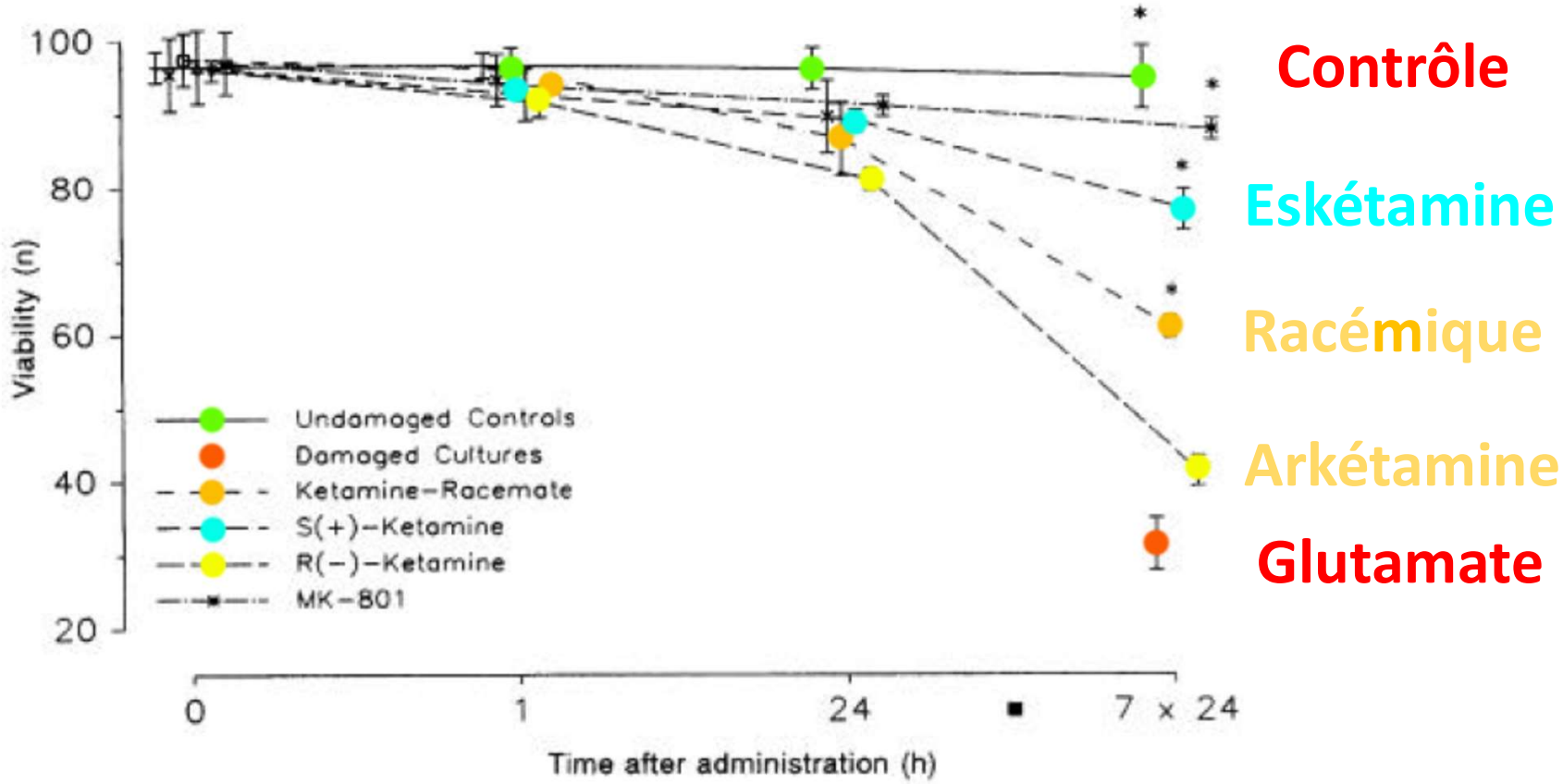


Figure 2. Survival of undamaged controls, glutamate-induced reduction in live cells of glutamate-exposed, untreated cultures, and glutamate-exposed cells treated with 10^{-4} M ketamine-racemate, 10^{-4} M S(+)-ketamine, 10^{-4} M R(−)-ketamine, and 10^{-6} M MK-801. Drugs were added after glutamate-exposure, and on postinjury

S(+)-ketamine/propofol maintain dynamic cerebrovascular autoregulation in humans

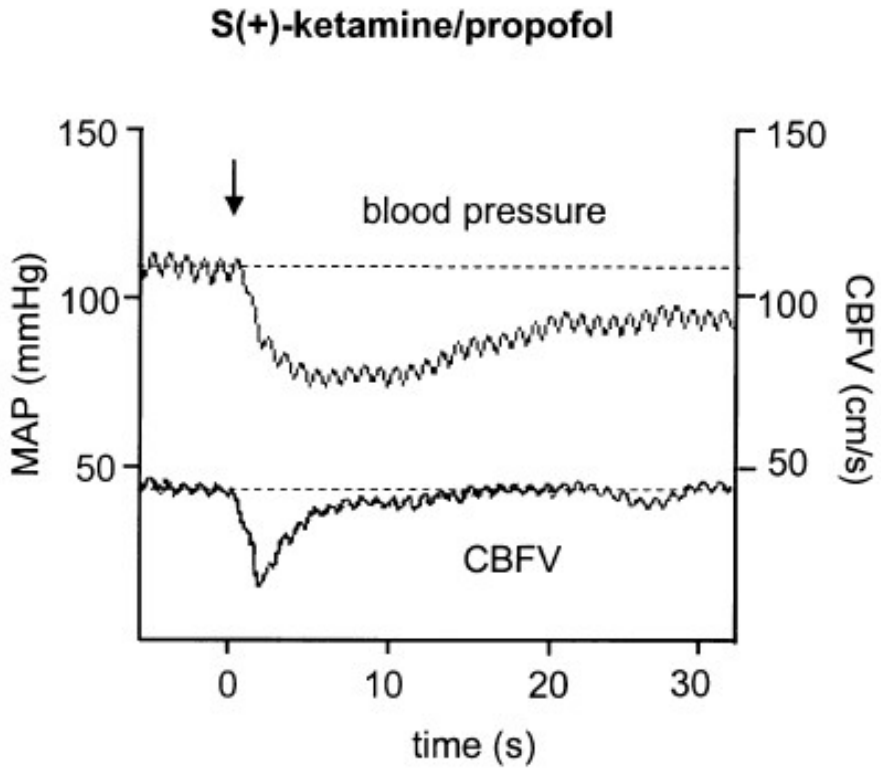
Kristin Engelhard MD, Christian Werner MD, Oliver Möllenberg MD, Eberhard Kochs MD

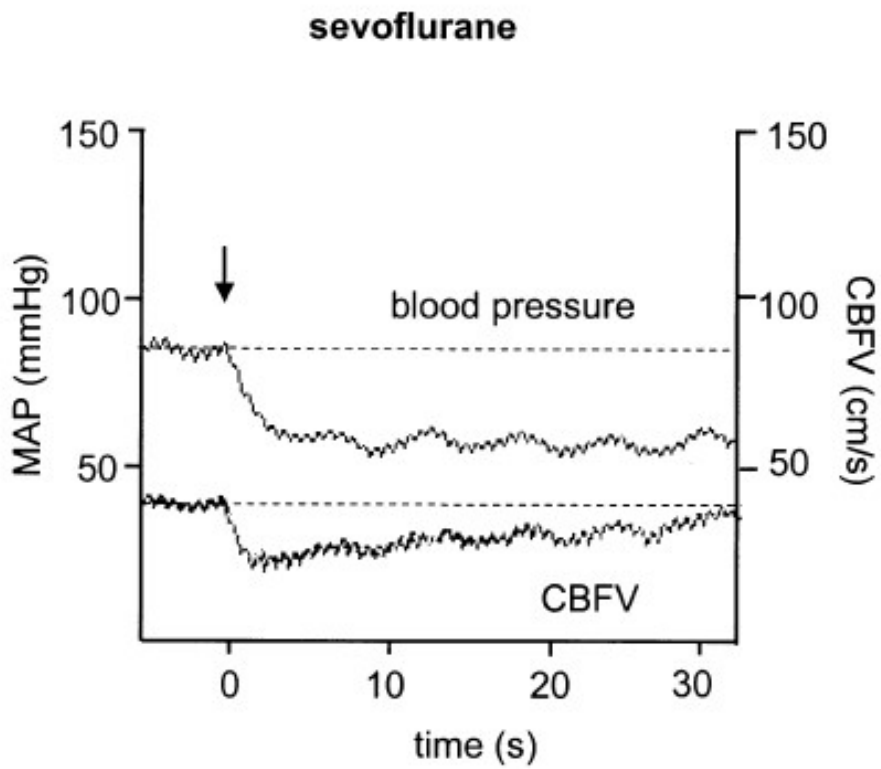
CAN J ANESTH 2001 / 48: 10 / pp 1034–1039

To assess dynamic cerebrovascular autoregulation the middle cerebral artery (MCA) blood flow velocity (CBFV) was measured by the transtemporal approach using a 2-MHz transcranial Doppler system (TCD,

was obtained in 24 patients (ASA physical status I–II) scheduled for elective abdominal surgery. Patients

To activate autoregulatory vasodilation a non-pharmacological sudden decrease in MAP of 15–20 mmHg was induced by rapid (<0.5 sec) deflation of large cuffs placed around both thighs, previously inflated to supra-systolic blood pressure levels for three minutes.[9,10] With





Effets neurocognitifs

Pharmacology of Ketamine Isomers in Surgical Patients

Paul F. White, M.D., Ph.D.,* Jay Ham, M.D.,† Walter L. Way, M.D.,‡ Anthony J. Trevor, Ph.D.§

Anesthesiology
52:231–239, 1980

equianesthetic doses of
racemic ketamine (RK), 2 mg/kg,
(+)ketamine (PK), 1 mg/kg, randomized,
(−)ketamine (MK), 3 mg/kg,
were administered intravenously to 60 healthy patients

double-blind

Patients received no premedicant

1980

The durations of anesthesia (35 ± 4 min) were the same in all three groups;

drug needed ranged from 2.4 mg/kg in the PK group
to 8.5 mg/kg in the MK group.

At the termination of anesthesia, mean plasma levels of the parent compounds were 0.9 (RK), 0.5 (PK), and 1.7 μg/ml (MK),
consistent with a PK:MK potency ratio of 3.4:1.

PK was judged to produce more effective anesthesia than RK or MK (95 *vs.* 75 *vs.* 68 per cent).

Verbal responses in the postanesthetic period suggested significantly
more psychic emergence reactions after MK than after RK or PK (37 *vs.* 15 *vs.* 5 per cent).

MK produced more agitated behavior than did RK or PK (26 *vs.* 10 *vs.* 0 per cent).

Postoperative pain occurred more commonly in the RK (10 per cent) and MK (16 per cent) groups than in the PK group (0 per cent).

The incidences of dreaming (84 per cent) were the same in all three groups.

The slopes of the plasma decay curves were not significantly different among the three groups.

similarities in the patterns of appearance and excretion of the ketamine metabolites suggest that the differences were due to pharmaco- dynamic factors.

Moins de douleur Avec l'eskétamine

Moins de problèmes d'émergence et d'agitaton avec l'eskétamine

Cognitive Impairment after Small-dose Ketamine Isomers in Comparison to Equianalgesic Racemic Ketamine in Human Volunteers

Ernst G. Pfenninger, M.D., Marcel E. Durieux, M.D., Ph.D.,† Sabine Himmelseher, M.D.‡*

Anesthesiology 2002; 96:357–66

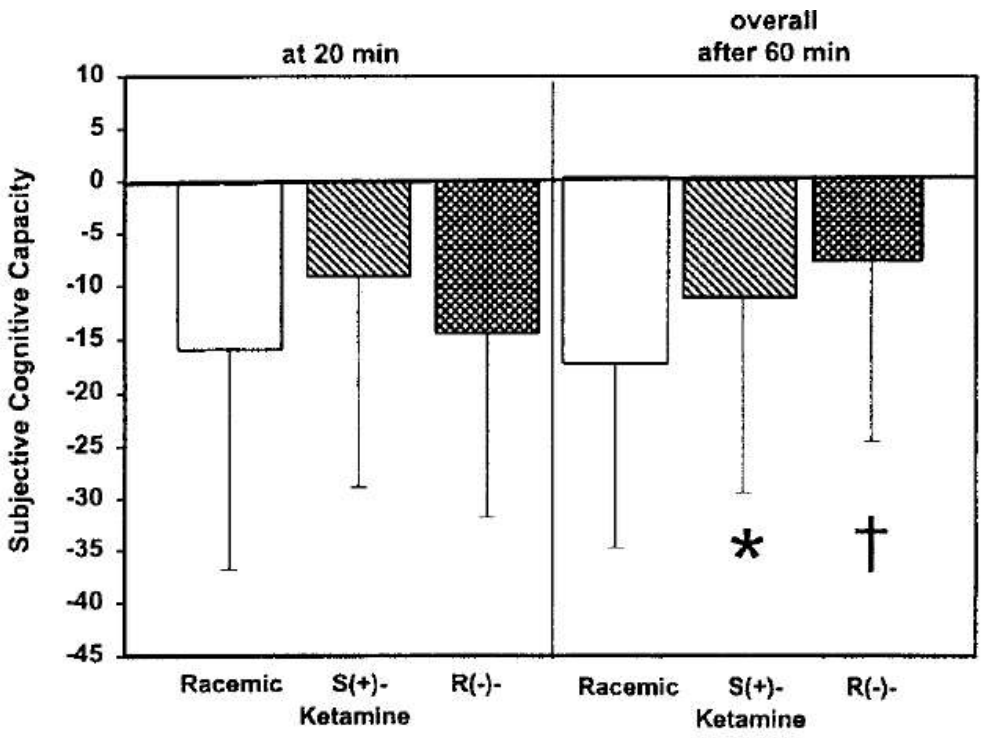
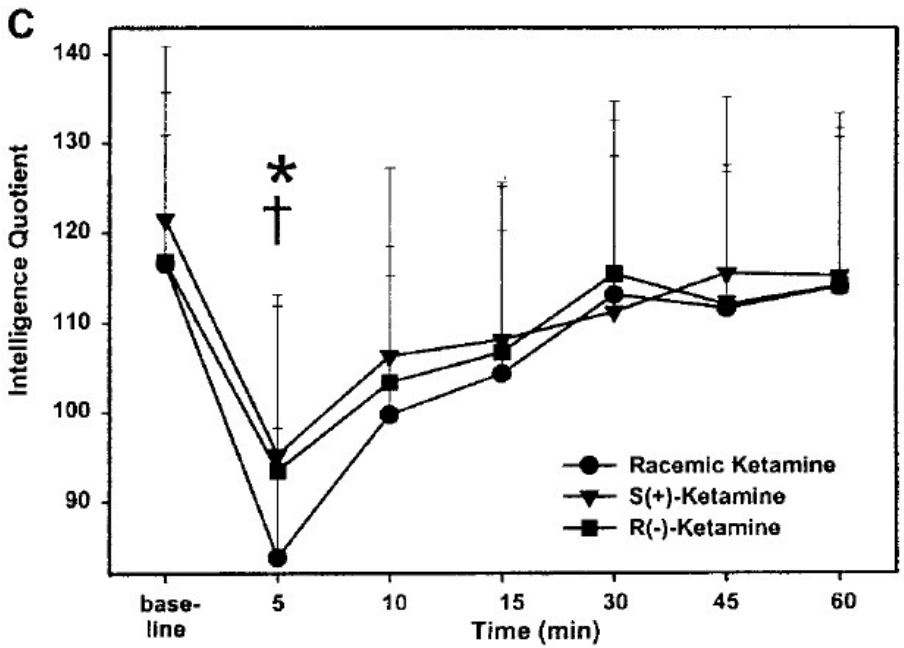


Fig. 3. Analysis of change of clustered rating scores for subjective cognitive capacity revealed less decline after $R(-)$- (P = 0.040) or $S(+)$-ketamine (P = 0.042) than after racemic ketamine for the overall period at 60 min. Bars show the mean ± SD. *Significant difference between racemic ketamine and $S(+)$-ketamine. †Significant diffference between racemic ketamine and $R(-)$-ketamine.

Methods: Twenty-four subjects received intravenous 0.5 mg/kg racemic, 0.25 mg/kg $S(+)$-, and 1.0 mg/kg $R(-)$-ketamine in a prospective, randomized, double-blind, crossover study. Hemodynamic variables, mood, and cognitive capacities were assessed for 60 min.



Plus de problèmes cognitifs avec le racémique

Comparison of Analgesic/Sedative Effect of Racemic Ketamine and S(+)-Ketamine during Cardiac Catheterization in Newborns and Children

C. Pees, N.A. Haas, P. Ewert, F. Berger, P.E. Lange

Pediatr Cardiol 24:424–429, 2003

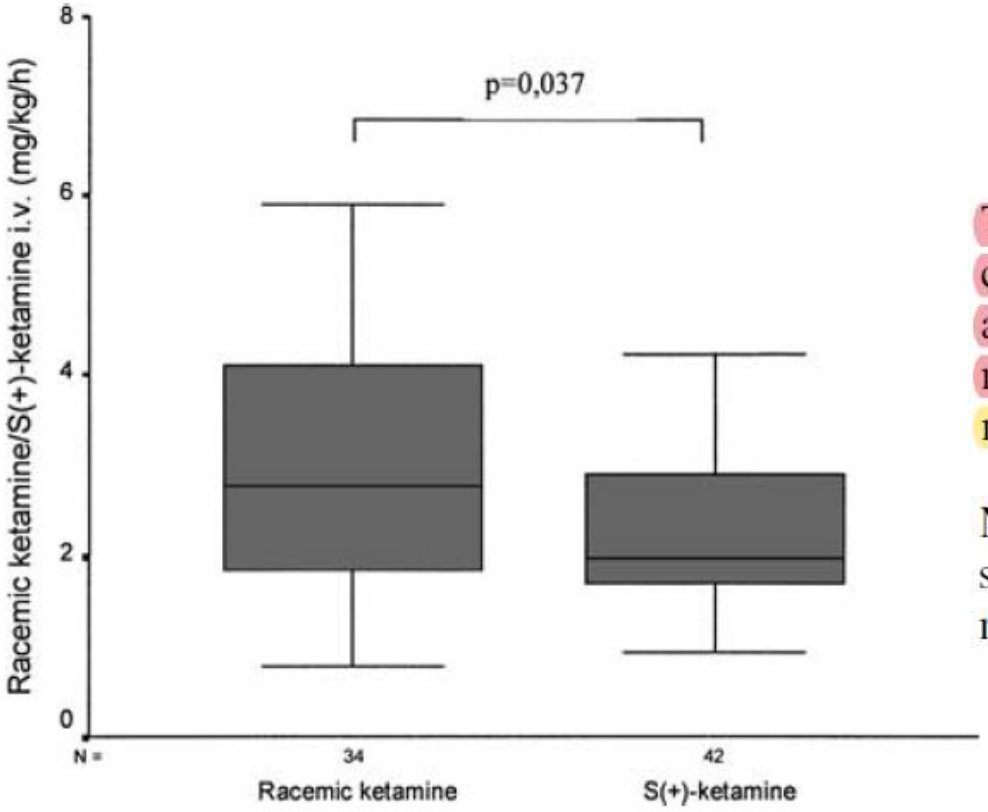


Fig. 1. Comparison of the necessary dosages of racemic ketamine and S(+)-ketamine in newborns and children during heart catheterization.

The average sleeping time after the last given medication was 127 min with racemic ketamine and midazolam compared to 96 min with S(+)-ketamine and midazolam, but statistical evaluation showed no significance, with an error estimation of 8.3%. Com-

Moderate side effects occurred in both groups; severe side effects seemed to occur more often with the racemic solution.

Comment interpréter Ces différences ?

Differential psychopathology and patterns of cerebral glucose utilisation produced by (*S*)- and (*R*)-ketamine in healthy volunteers using positron emission tomography (PET)

F.X. Vollenweider[a,*], K.L. Leenders[b], I. Øye[c], D. Hell[a], J. Angst[a]

European Neuropsychopharmacology 7 (1997) 25–38

reported here. Psychotomimetic doses of (*S*)-ketamine increased cerebral metabolic rates of glucose (CMRglu) markedly in the frontal cortex including the anterior cingulate, parietal and left sensorimotor cortex, and in the thalamus. The metabolic changes in the frontal and left temporal cortex correlated with ego-disintegration and hallucinatory phenomena. Equimolar doses of (*R*)-ketamine tended to decrease CMRglu across brain regions and significantly suppressed CMRglu in the temporomedial cortex and left insula. (*R*)-ketamine did not produce psychotic symptoms, but a state of relaxation. The (*S*)-ketamine-induced metabolic hyperfrontality appears to parallel similar metabolic findings in acute psychotic schizophrenic patients and encourages further investigations of glutamatergic disturbances in schizophrenia. © 1997 Elsevier Science B.V. All rights reserved.

Les effets psychomimétiques dépendent de l'inhibition des R-NMDA

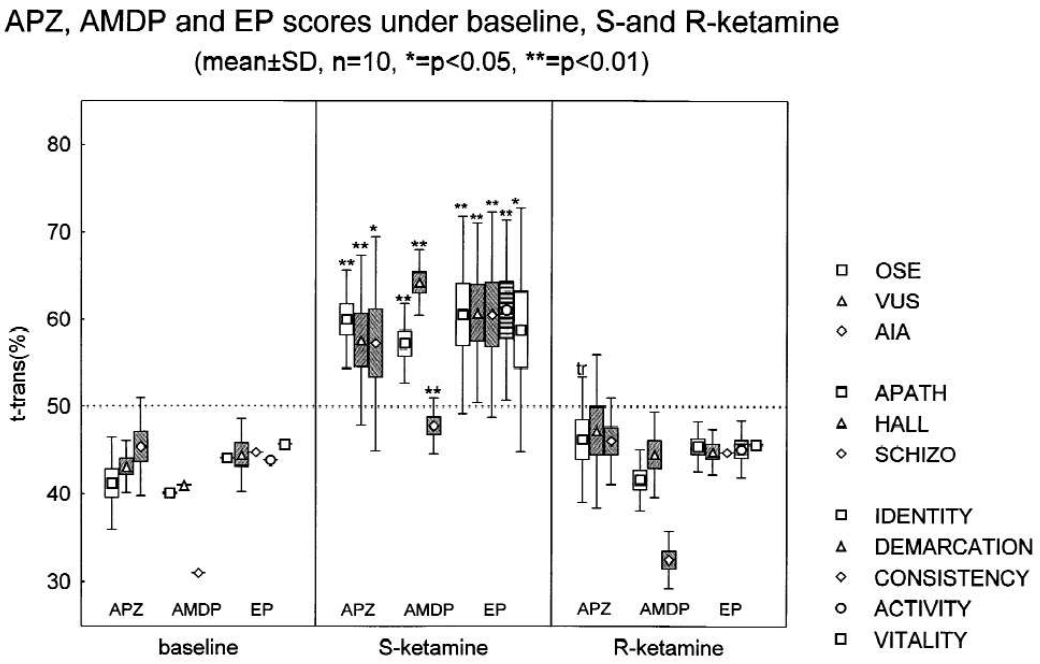


Fig. 1. Mean scores of selected APZ, AMDP and EPI subscales under baseline, (*S*)- and (*R*)-ketamine conditions during PET scanning (mean±S.D.). While (*S*)-ketamine administration resulted in a psychosis-like syndrome, equimolar doses of (*R*)-ketamine produced a state of relaxation as indicated by the slight, but only marginal increase of the APZ subscale score for OSE (oceanic boundlessness) (tr: $P=0.06$). Boxes indicate mean±S.E., significant changes are indicated by Wilcoxon's, $*P<0.05$, $**P<0.01$).

Pharmacodynamie

- **Inhibition** non compétitive **NMDA-R**
- **Inhibition** des canaux **HCN1** (I*h*)
- **Effet anticholinergique central** (SAC)
- **Anticalcique** (dilatation bronches et vaisseaux)
- **Activation syst. monoaminergiques desc.**
- **Effet anesthésique local** (canaux sodiques)
- **Effets anti-proinflammatoires** (**NfκB**)
- **Effets antidépresseurs**

M. BEECH
C. HELL
P. NIGHTINGALE

The patient responded only to painful stimulation. His blood pressure was 130/80 mm Hg and pulse 130/min. The skin was warm and dry and his axillary temperature 37·5°C. There were no focal neurological signs but the pupils were dilated. A diagnosis of CAS was suggested and physostigmine salicylate 1 mg was slowly injected intravenously. Within 2 min the patient regained full consciousness. He remained sleepy for several hours but was easily rousable. The rest of his hospital recovery was uneventful. There

Physostigmine Antagonizes Ketamine

TORO-MATOS, A., RENDON-PLATAS, A. M., AVILA-VALDEZ, E., AND VILLARREAL-GUZMAN, R. A.

Anesth Analg 59:764–767, 1980.

In a random cross-over double-blind trial, the effects of intravenous physostigmine salicylate (2.0 mg) and placebo were observed in seven healthy volunteers 10 minutes after the intravenous administration of 1.5 mg/kg of ketamine. Recovery time was significantly shorter after physostigmine than after placebo. Nystagmus and blurred vision, which followed ketamine anesthesia, disappeared more rapidly when physostigmine was given. This study confirms previous observations that physostigmine counteracts some of the manifestation of ketamine aftereffects which resemble the so-called central anticholinergic syndrome. Nausea and vomiting were significantly more frequent after physostigmine administration.

Nonstereoselective Inhibition of Neuronal Nicotinic Acetylcholine Receptors by Ketamine Isomers

(Anesth Analg 2000;91:741–8)

Toshio Sasaki, MD, Tomio Andoh, MD, PhD, Itaru Watanabe, MD, Yoshinori Kamiya, MD, Hideki Itoh, MD, Tomoko Higashi, MD, and Takayuki Matsuura, MD

These results indicate that the inhibitory action of ketamine isomers on neuronal nAchRs is not stereoselective. Although our findings do not deny possible involvement of these receptors in ketamine anesthesia, they suggest that inhibition of neuronal nAchRs is not primarily responsible for the anesthetic action of this anesthetic.

Synergistic Inhibition of Muscarinic Signaling by Ketamine Stereoisomers and the Preservative Benzethonium Chloride

Marcel E. Durieux, M.D., Gregor W. Nietgen, M.D.†*

Anesthesiology
1997; 86:1326–33

Methods: **Rat m1 muscarinic acetylcholine receptors were expressed recombinantly in *Xenopus laevis* oocytes.**

Results: **The IC_{50} was 125 ± 33 μM for S(+) ketamine, and 91 ± 19 μM for R(−) ketamine. This difference was not statistically significant, indicating that muscarinic inhibition by ketamine is not stereoselective. The R(−)/S(+) mixture had an IC_{50} of 48 ± 1 μM, and thus the stereoisomers interact synergistically.**

Différences pharmacocinétiques

Pharmacokinetics of ketamine and its major metabolites norketamine, hydroxynorketamine, and dehydronorketamine: a model-based analysis

Jasper Kamp*, Kelly Jonkman, Monique van Velzen, Leon Aarts, Marieke Niesters, Albert Dahan and Erik Olofsen

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Abstract

Background: Recent studies show activity of ketamine metabolites, such as hydroxynorketamine, in producing rapid relief of depression-related symptoms and analgesia. To improve our understanding of the pharmacokinetics of ketamine and metabolites norketamine, dehydronorketamine, and hydroxynorketamine, we developed a population pharmacokinetic model of ketamine and metabolites after i.v. administration of racemic ketamine and the S-isomer (esketamine). Pharmacokinetic data were derived from an RCT on the efficacy of sodium nitroprusside (SNP) in reducing the psychotomimetic side-effects of ketamine in human volunteers.

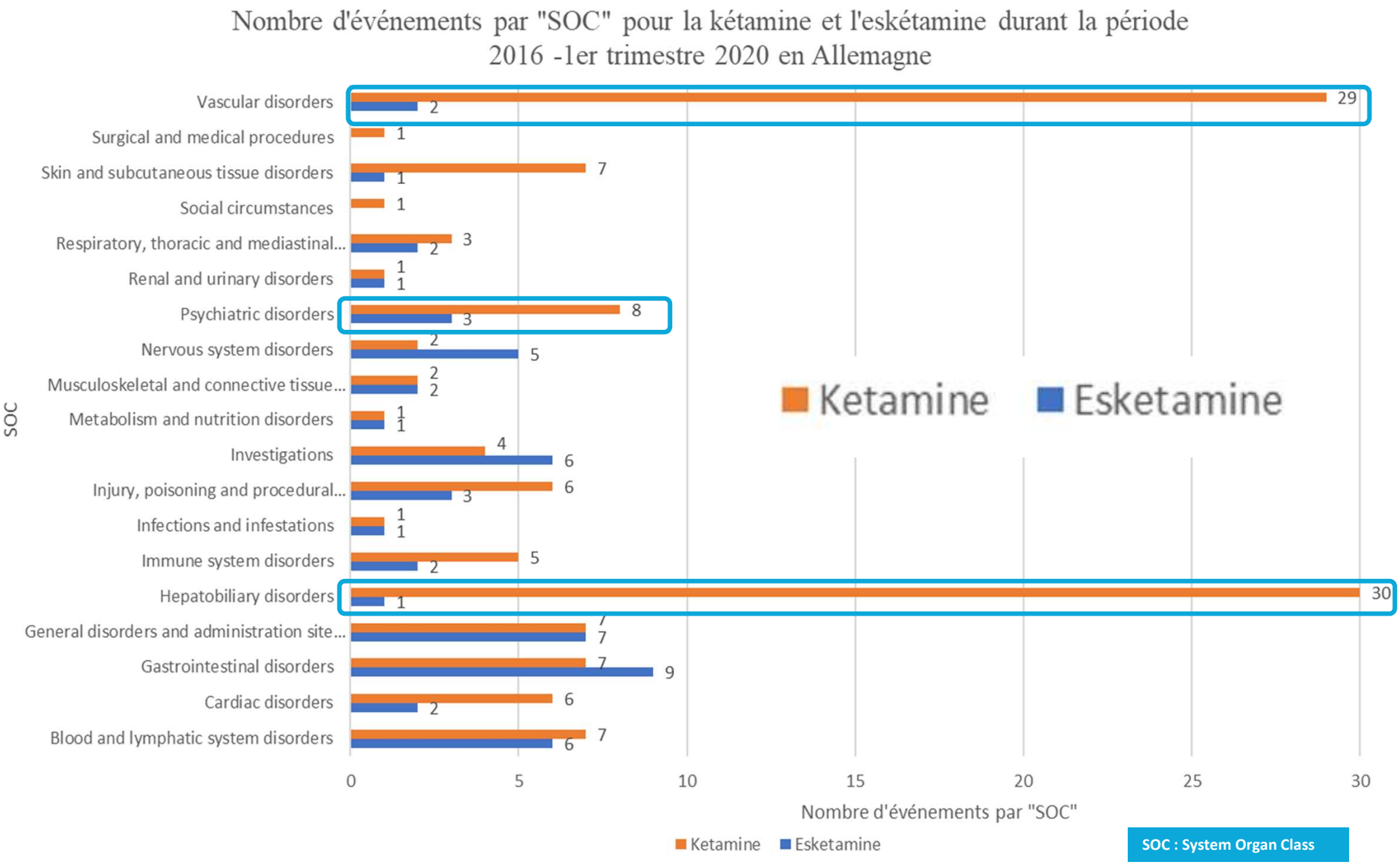
Methods: Three increasing i.v. doses of esketamine and racemic ketamine were administered to 20 healthy volunteers, and arterial plasma samples were obtained for measurement of ketamine and metabolites. Subjects were randomised to receive esketamine/SNP, esketamine/placebo, racemic ketamine/SNP, and racemic ketamine/placebo on four separate occasions. The time–plasma concentration data of ketamine and metabolites were analysed using a population compartmental model approach.

Results: The pharmacokinetics of ketamine and metabolites were adequately described by a seven-compartment model with two ketamine, norketamine, and hydroxynorketamine compartments and one dehydronorketamine compartment with metabolic compartments in-between ketamine and norketamine, and norketamine and dehydronorketamine main compartments. Significant differences were found between S- and R-ketamine enantiomer pharmacokinetics, with up to 50% lower clearances for the R-enantiomers, irrespective of formulation. Whilst SNP had a significant effect on ketamine clearances, simulations showed only minor effects of SNP on total ketamine pharmacokinetics.

Conclusions: The model is of adequate quality for use in future pharmacokinetic and pharmacodynamic studies into the efficacy and side-effects of ketamine and metabolites.

Clinical trial registration: Dutch Cochrane Center 5359.

Données de pharmacovigilance (Allemagne)



SOC : System Organ Class

Conclusion

- différence essentielle : **l'eskétamine est deux fois plus active** que le racémique en termes d'analgésie et de narcose
- L'eskétamine a un **meilleur profil sur les systèmes circulatoire et nerveux**
- l'eskétamine a une **clairance plus élevée** que le racémique. Dans plusieurs études cliniques, cet avantage s'est accompagné d'une émergence plus rapide et plus calme
- des doses deux fois moindres d'eskétamine laissent espérer une **diminution potentielle de la toxicité** notamment en cas d'administration prolongée

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ESKÉTAMINE

A propos de la **note eskétamine de la SFAR**

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Mion G
Eskétamine
Conférence 2023

***

Mion G
Histoire des antagonistes NMDA et perspectives.
Conférence au symposium CDM LAVOISIER / IDD, congrès annuel de la SFAR, Paris, 22 septembre 2022.

***

Proposition de **protocoles d'utilisation** (respectant l'AMM)

Proposition de protocoles **pour la douleur chronique** (hors AMM)

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Bibliographie sur Pubmed

Merci