Eskétamine

Georges Mion
Cochin (Paris)

Centre Hospitalier de Haguenau

12 Mars 2026

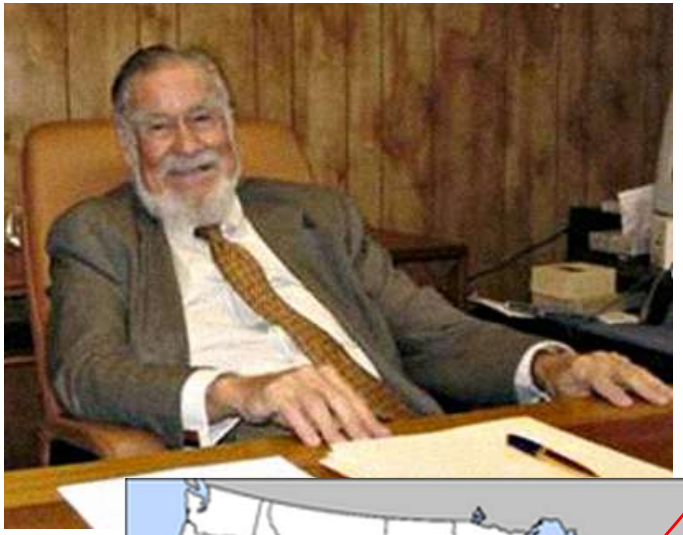
Notre itinéraire

- **Pharmacologie**
  - PK/PD
  - Antagonisme du NMDA-R
- **Différences entre S+ et R- kétamines**
  - Puissances anesthésique/analgésique
  - Effets neurocognitifs
  - Effets cardiaques - cérébraux
- **Expérience clinique**
  - Anesthésie, sédation, analgésie
  - Réanimation, toxicité

Georges Mion est consultant pour International Drug Development (IDD)

EXPLOITATION ET STRATÉGIE RÉGLEMENTAIRE

Notre cœur de métier : le dossier d'AMM



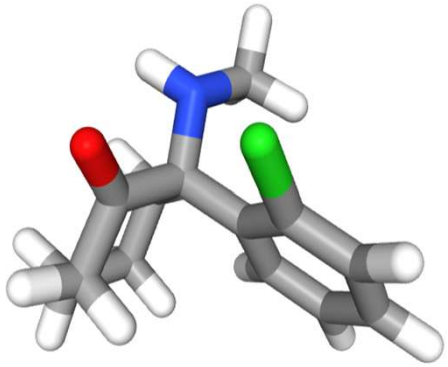
Calvin Stevens (1923-2014)

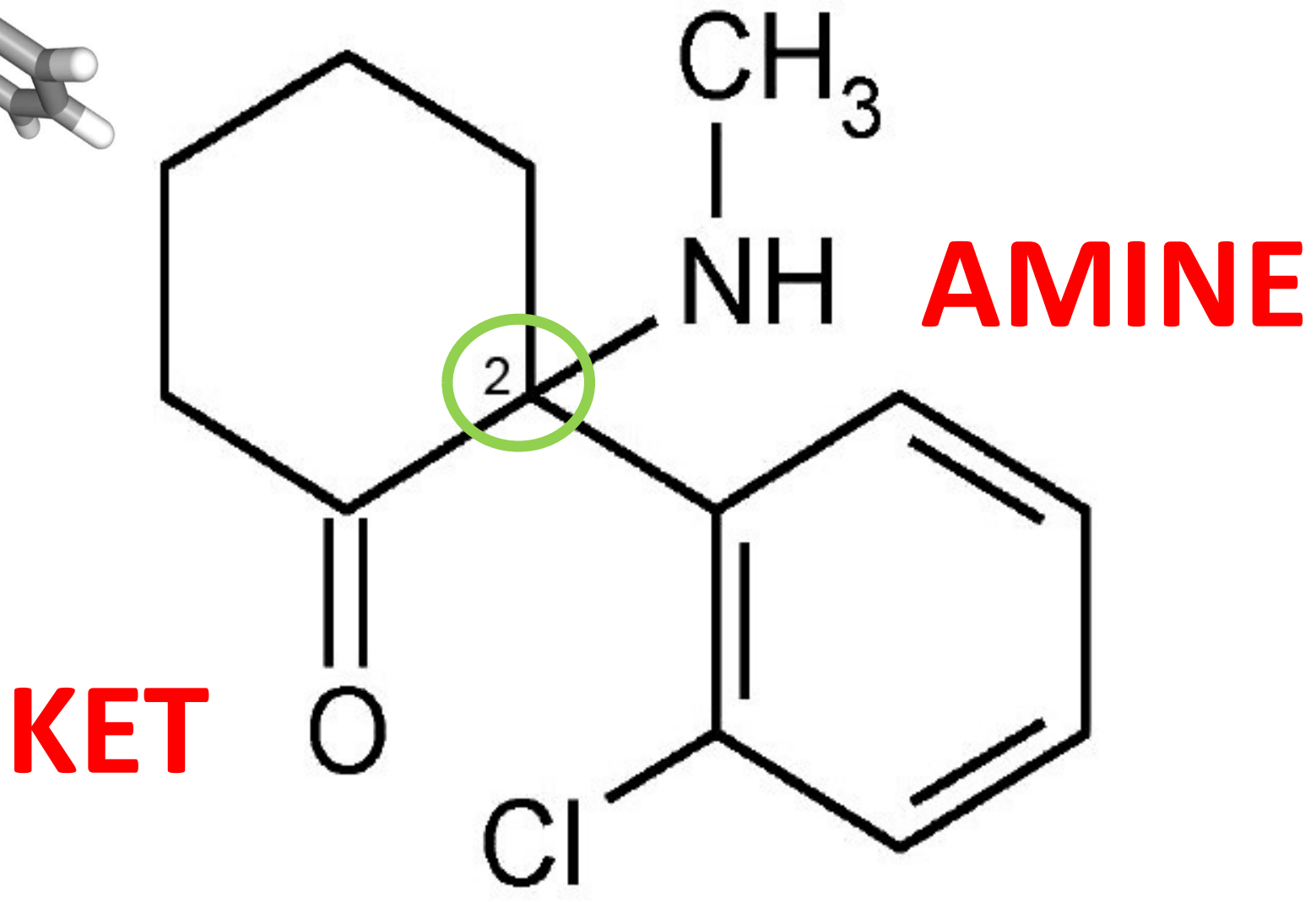
professeur de chimie à l'université de Wayne (Michigan)

synthétise le CI-581

aux laboratoires Parke Devis

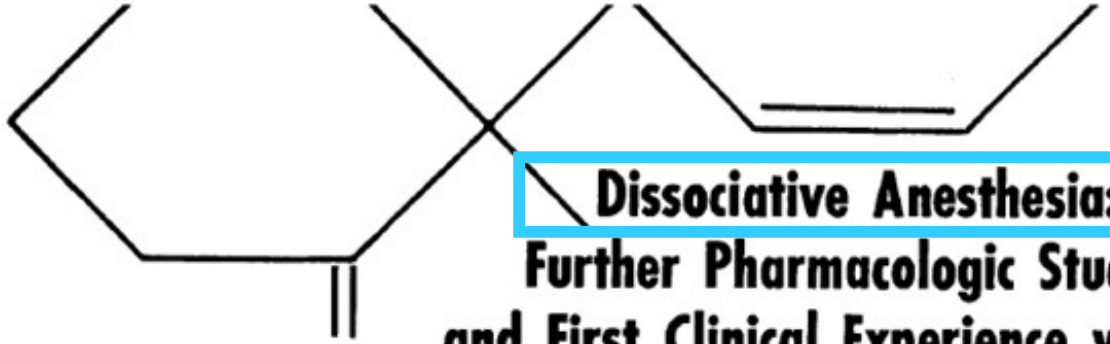
2 - ortho-chlorophényl - 2 - méthylamino - cyclohexanone





Edward F. Domino, Ph.D. (1924–2021)

ANESTHESIA and ANALGESIA VOL. 45, NO. 1 1966



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

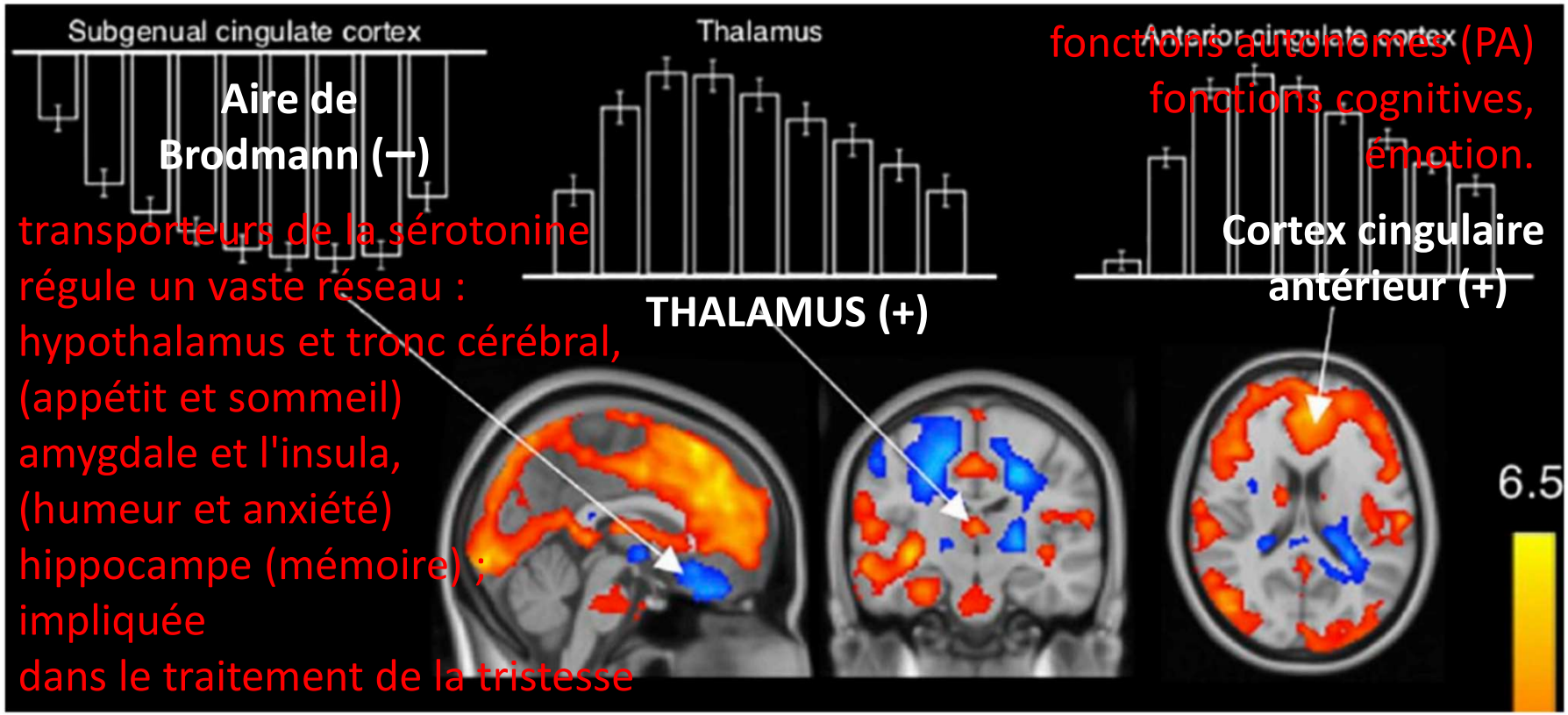
GUENTER CORSSEN, M.D.
EDWARD F. DOMINO, M.D.
Ann Arbor, Michigan*

ANESTHESIE « DISSOCIATIVE »

Temporal dynamics of the pharmacological MRI response to subanaesthetic ketamine in healthy volunteers: A simultaneous EEG/fMRI study

Journal of Psychopharmacology
1–11 2019

Rebecca McMillan[1], Anna Forsyth[1], Doug Campbell[2], Gemma Malpas[2], Elizabeth Maxwell[2], Juergen Dukart[3,4,5], Joerg F Hipp[3] and Suresh Muthukumaraswamy[1]



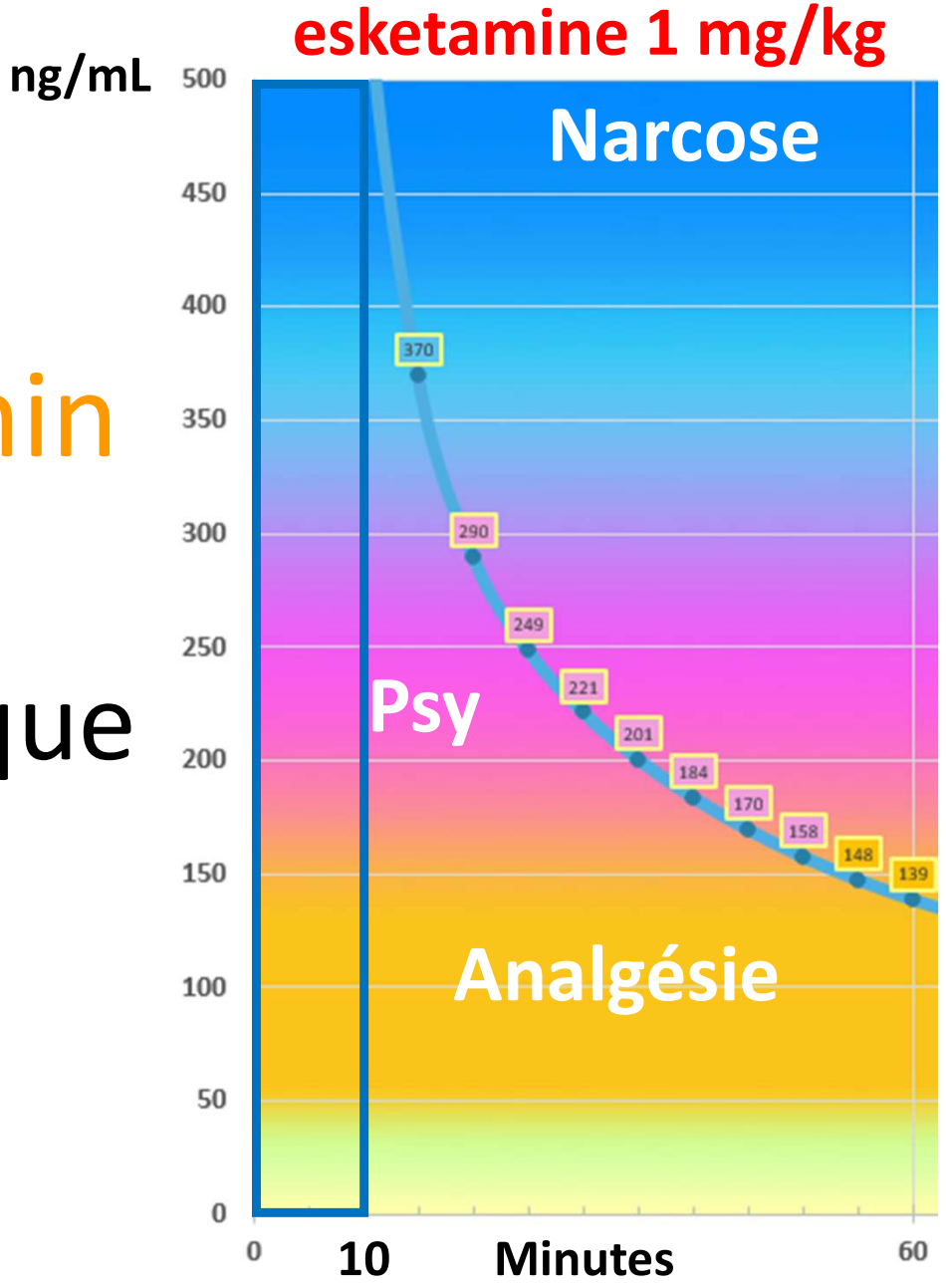
transporteurs de la sérotonine
régule un vaste réseau :
hypothalamus et tronc cérébral,
(appétit et sommeil)
amygdale et l'insula,
(humeur et anxiété)
hippocampe (mémoire) ;
impliquée
dans le traitement de la tristesse

fonctions autonomes (PA)
fonctions cognitives,
émotion.

Figure 2. Group maps showing the locations of significant (*F*-ratio maps, $p < 0.05$, familywise error (FWE) cluster corrected) effects of ketamine on the blood-oxygenation-level-dependent (BOLD) signal during the first 9 minutes of ketamine infusion. Although these are *F*-ratio maps, for visual display purposes, areas that showed decreased BOLD responses post-hoc are coloured blue. A grey matter mask was applied to all maps. The histograms show the time series of the BOLD signal change in 1-minute increments from three selected regions showing a significant effect of ketamine. Error bars represent 90% confidence intervals.

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-eskétamine



Pharmacodynamie

- **Inhibition** non compétitive **NMDA-R**
- **Inhibition** des canaux **HCN1** (*Hyperpolarisation-activated Cyclic-Nucleotid* 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** (**BDNF**)
- **……. dopamine, sérotonine, sigmaR, mTor, BDNF-TrkB…**

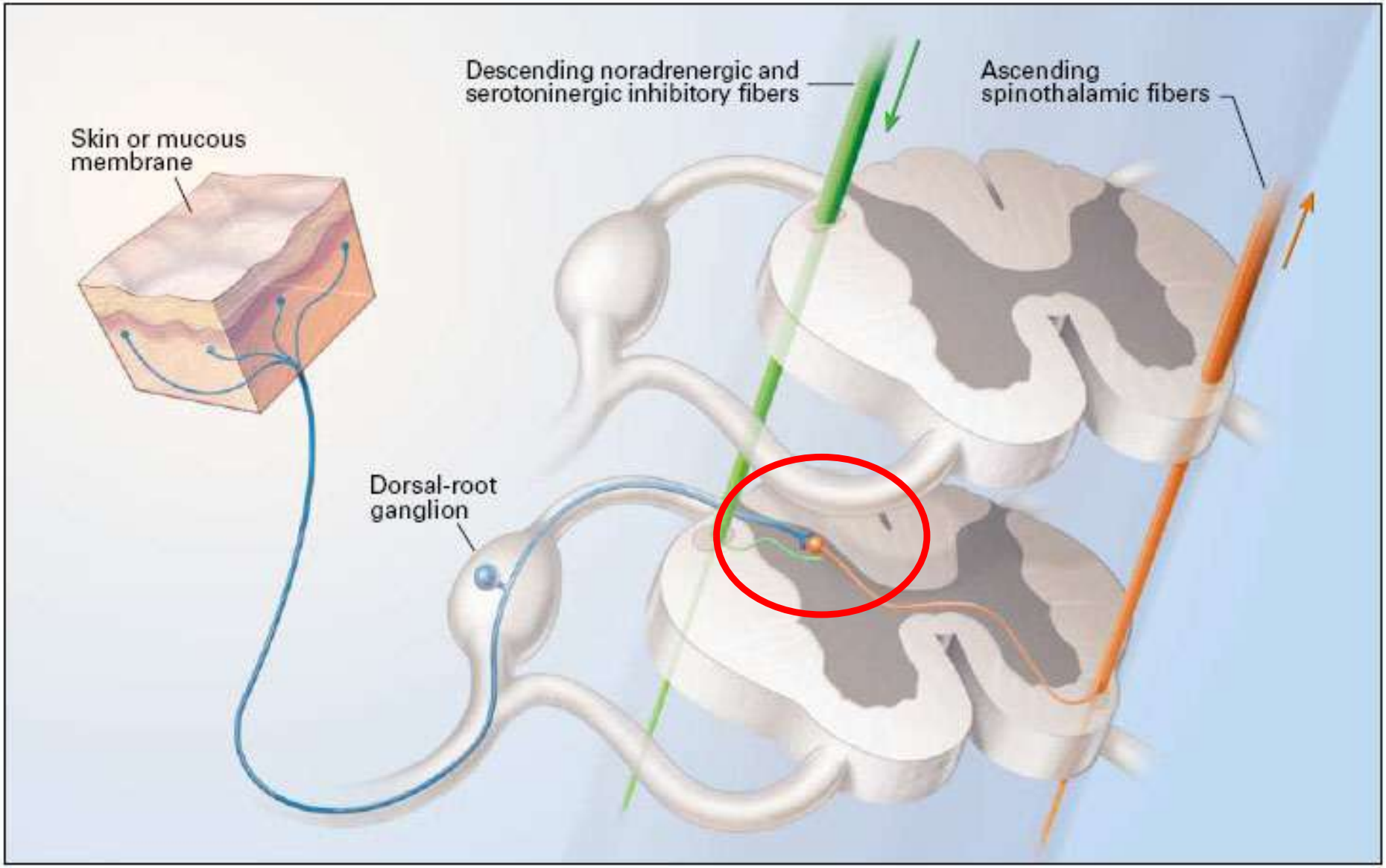
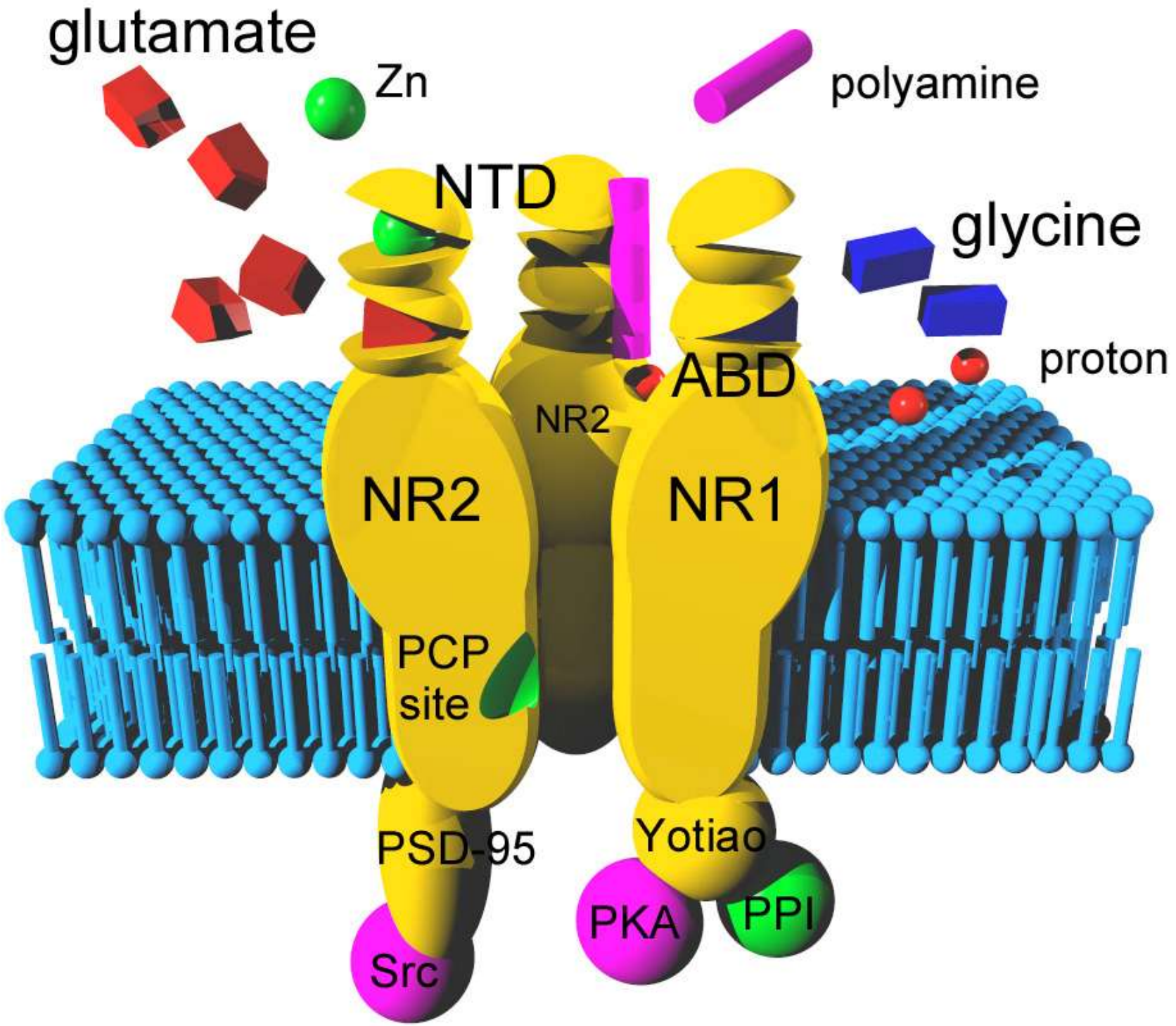


Figure 3. Pathway of Normal Pain Perception.

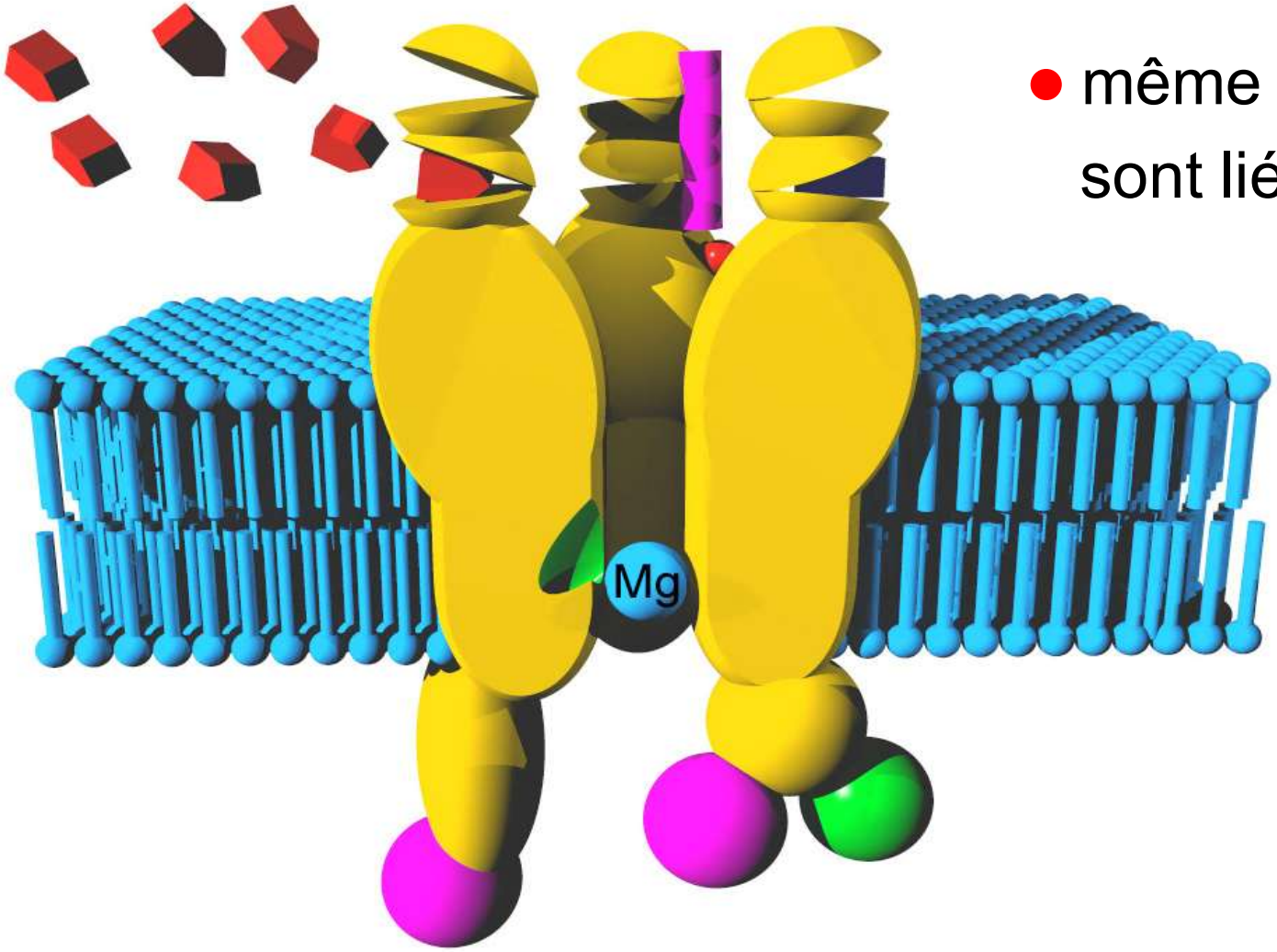
Noxious stimuli activate free nerve endings in the skin to generate signals that are conveyed through unmyelinated C fibers (blue) and small Aδ fibers to the neuronal bodies in the segmental dorsal-root ganglia, then proximally to the dorsal horn of the spinal cord, where they form synapses with second-order neurons.[66] Spinal cord neurons are subject to powerful descending inhibitory signals from the brain (green), mediated by the biogenic amines serotonin and norepinephrine. Drugs that potentiate the central effects of biogenic amines, such as tricyclic antidepressant drugs, may act by enhancing these descending pathways.[66] Endogenous opiates also contribute to descending inhibitory input. The net result of peripheral afferent input and descending inhibitory input is projected cephalad, joining other ascending fibers in the contralateral spinothalamic tract (orange). Information from the spinothalamic tract is integrated with input from brain-stem and cortical areas for the perception of specific aspects of pain, as well as more general affective components of pain perception.


glutamate
Zn
polyamine
NTD
glycine
proton
ABD
NR2
NR2
NR1
PCP
site
PSD-95
Yotiao
PKA
PPI
Src

Bloc magnésien *voltage-dépendant*

- quand la membrane est polarisée

  les ions Mg^{2+} obstruent le canal



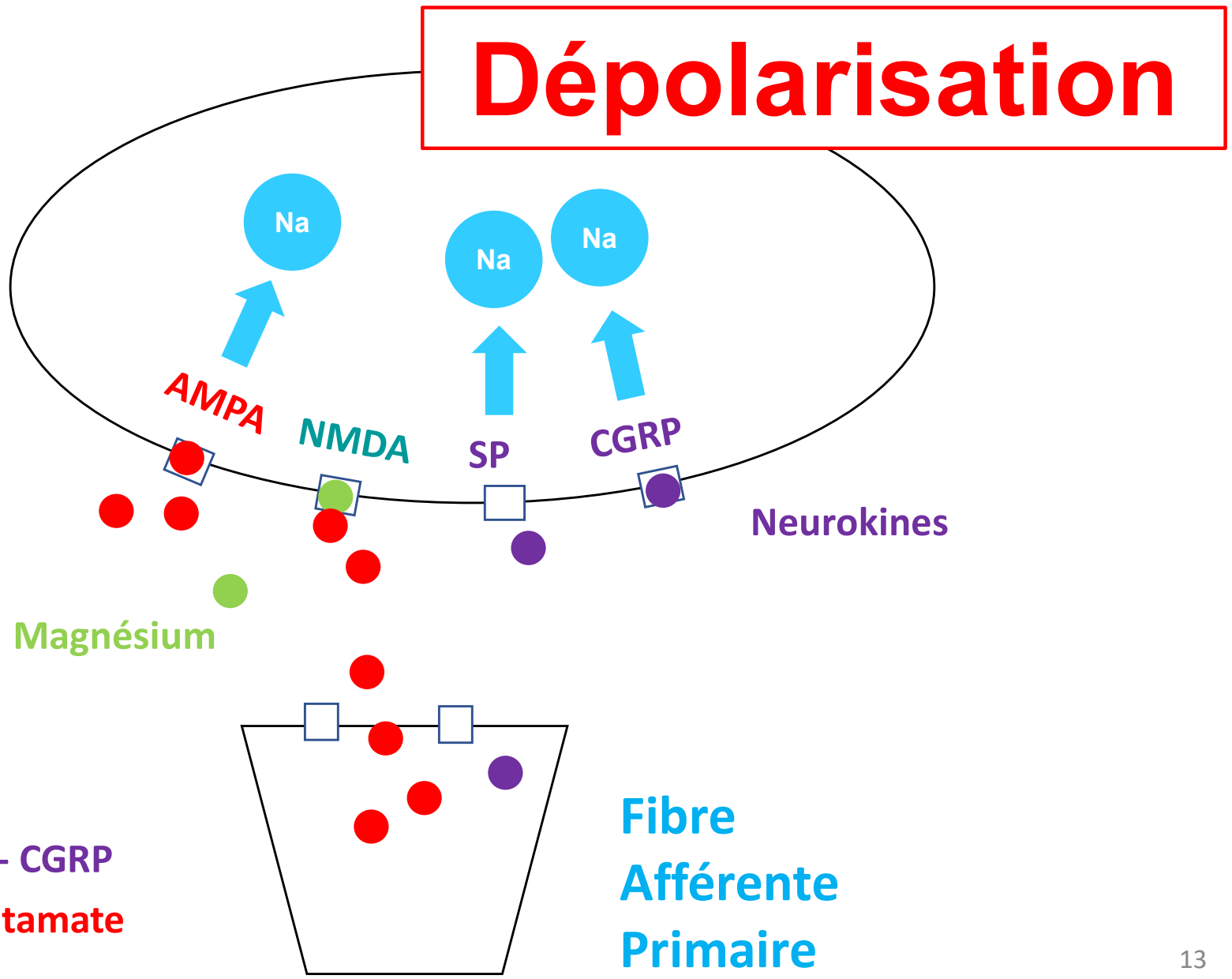
- même si les co-agonistes sont liés au récepteur

Bloc magnésien voltage-dépendant

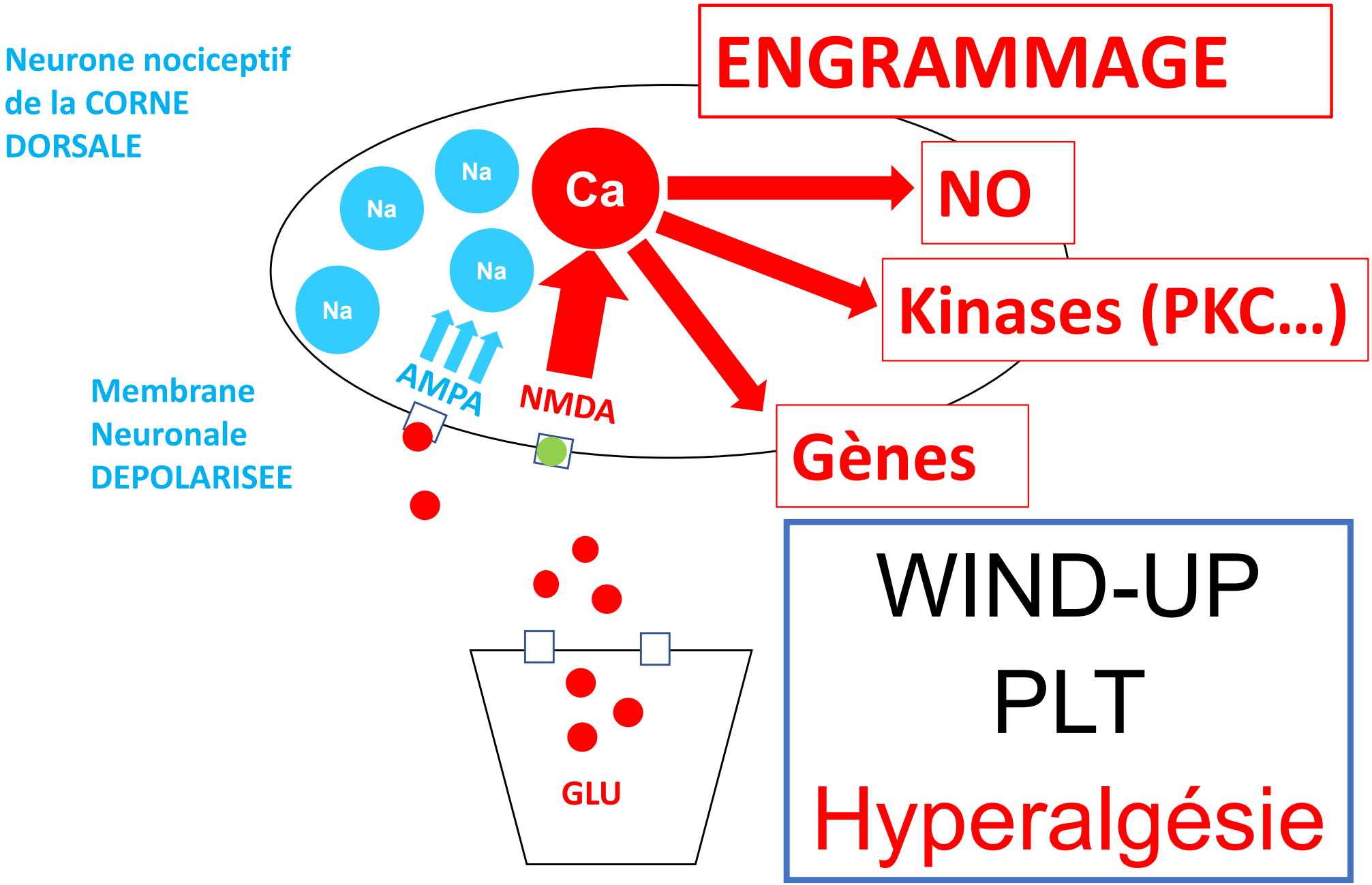
Glutamate : AMPA et NMDA

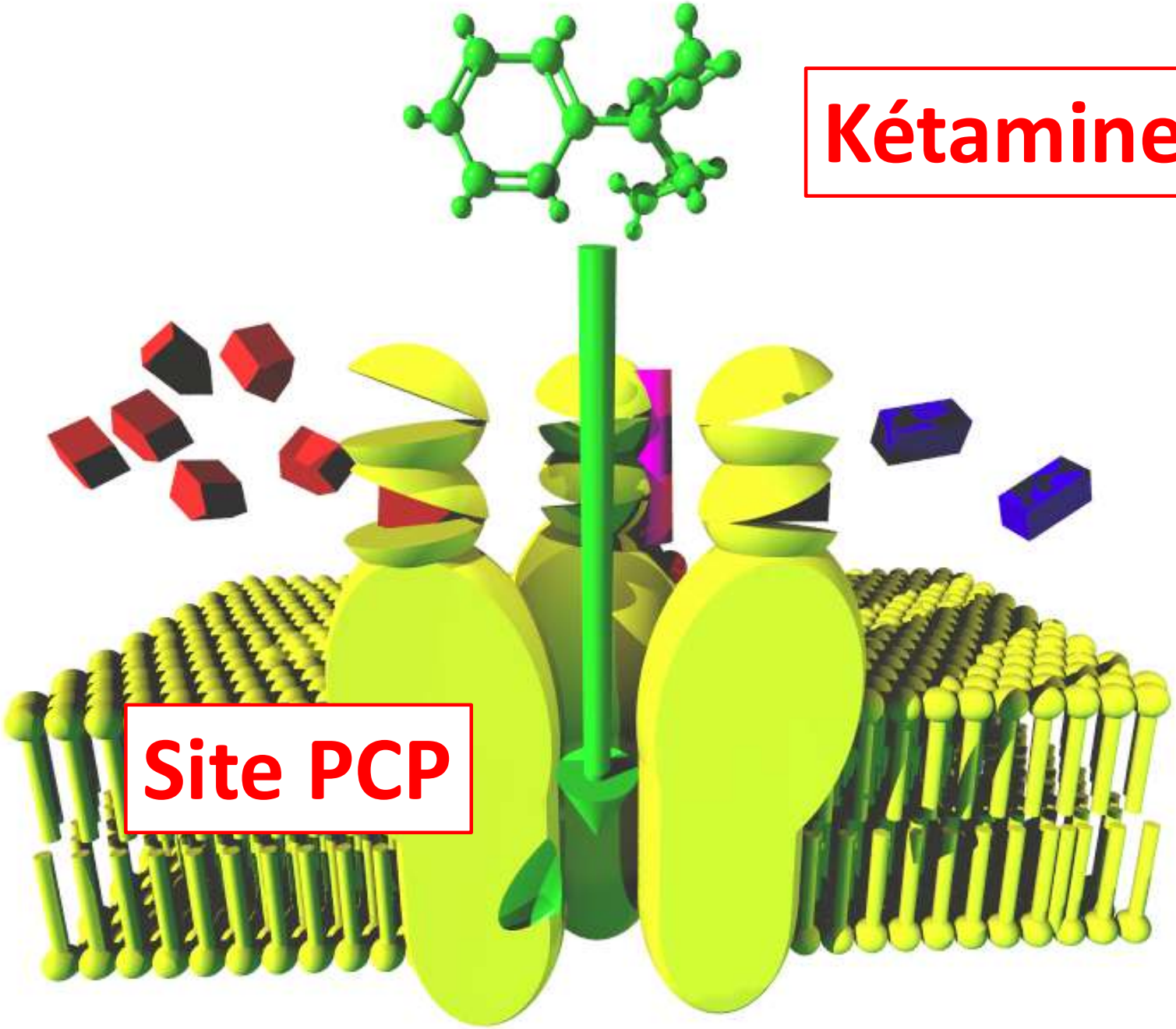
Neurone nociceptif de la CORNE DORSALE

α-amino
-3-hydroxy
-5-methyl
-4-isoxazole
propionic acid



Si la membrane est dépolarisée





Use dependance

Que veut dire

?

2 énantiomères

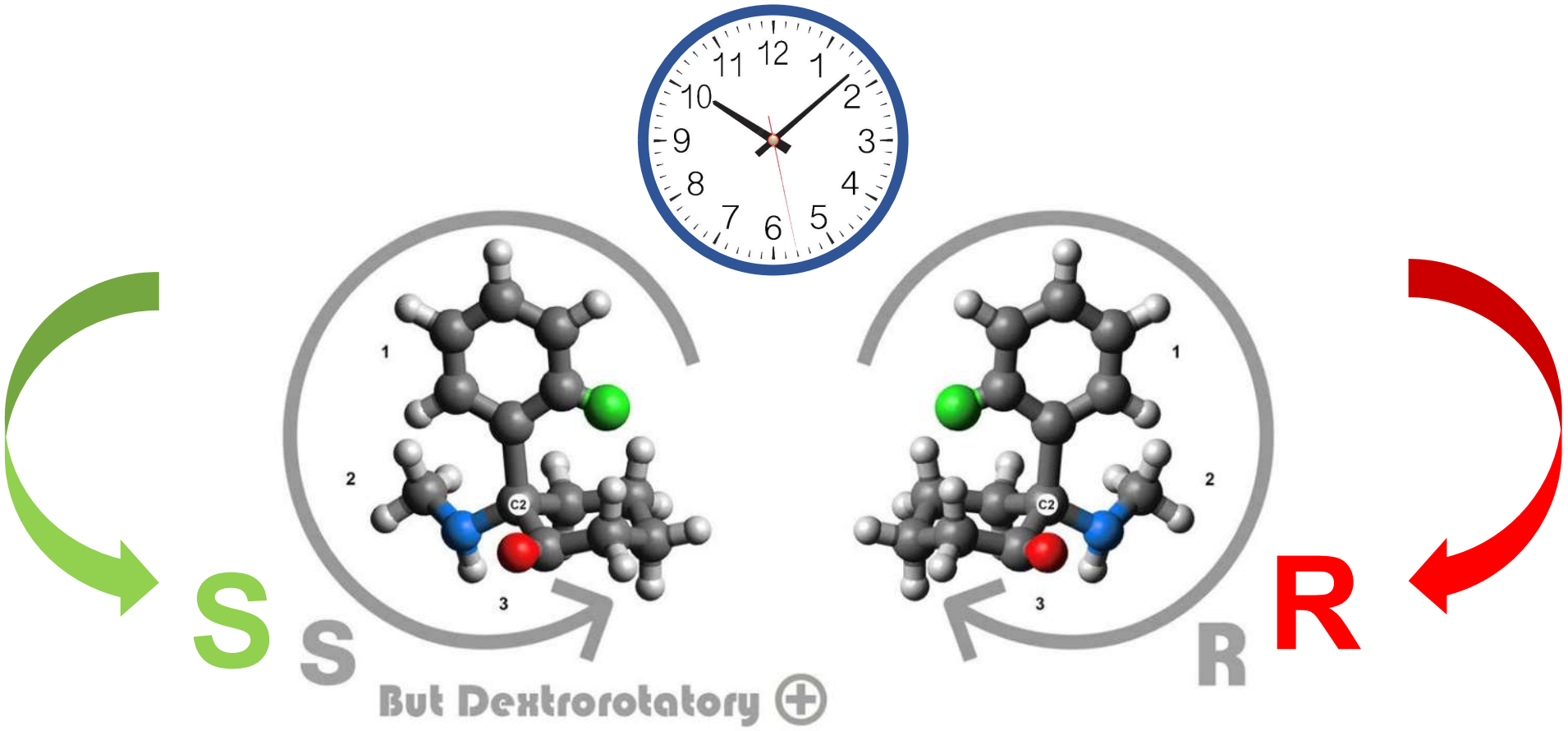
S(+) dextrogyre

vs **R(-) lévogyre**

Esketamine: Less Drowsiness, More Analgesia

Georges Mion, MD* and Sabine Himmelseher, MD†

Anesth Analg January 31, 2024.



AMM 2020

HAUTE AUTORITÉ DE SANTÉ

COMMISSION DE LA TRANSPARENCE

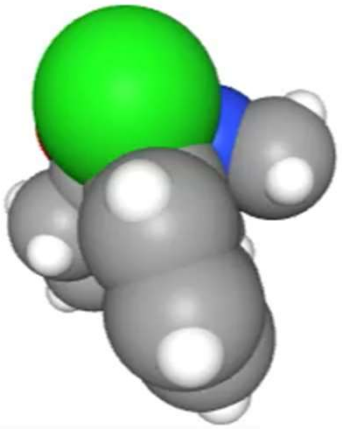
21 JUILLET 2021

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).



Eskétamine
la clé du NMDA-R

NMDA-R

Arkétamine

Eskétamine

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

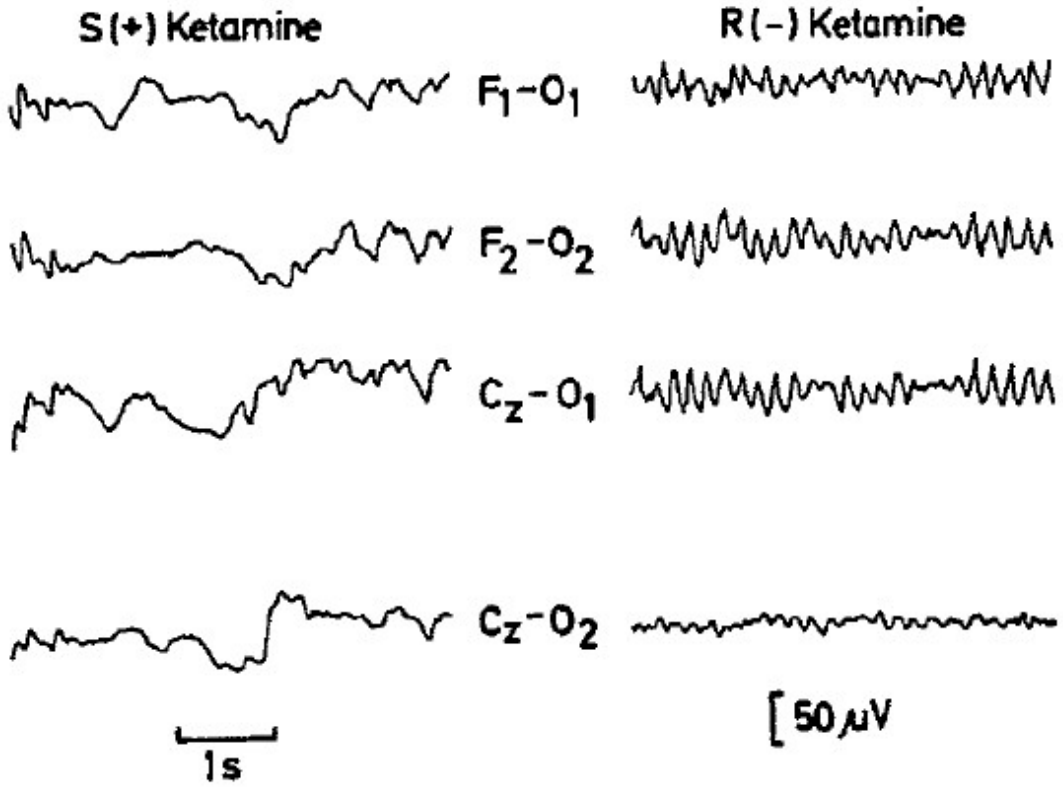


FIG. 2. A typical four-lead EEG pattern demonstrating the *maximal* slowing during or immediately after the infusion of S(+) ketamine or the R(−) isomer i.v.

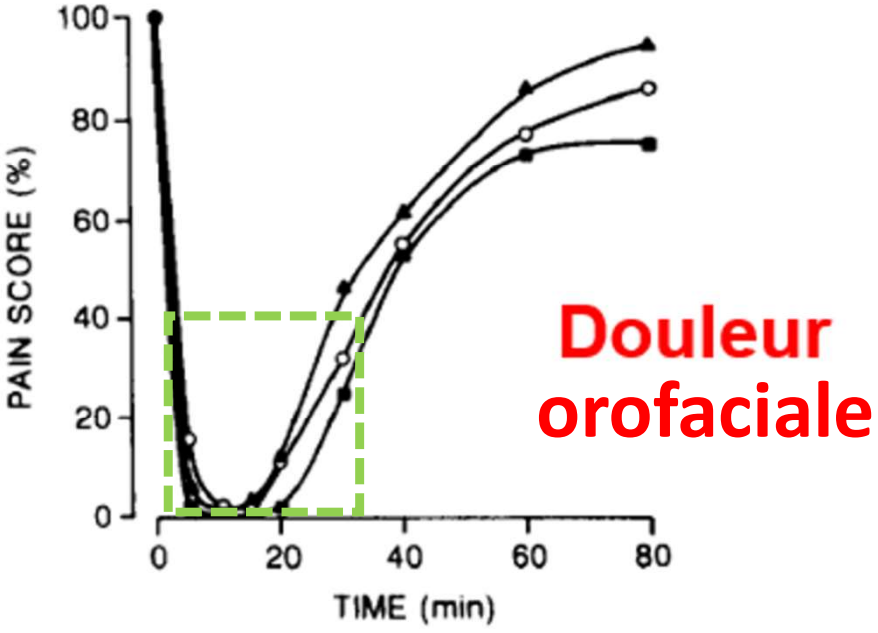
Effect of ketamine, an NMDA receptor inhibitor, in acute and chronic orofacial pain

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

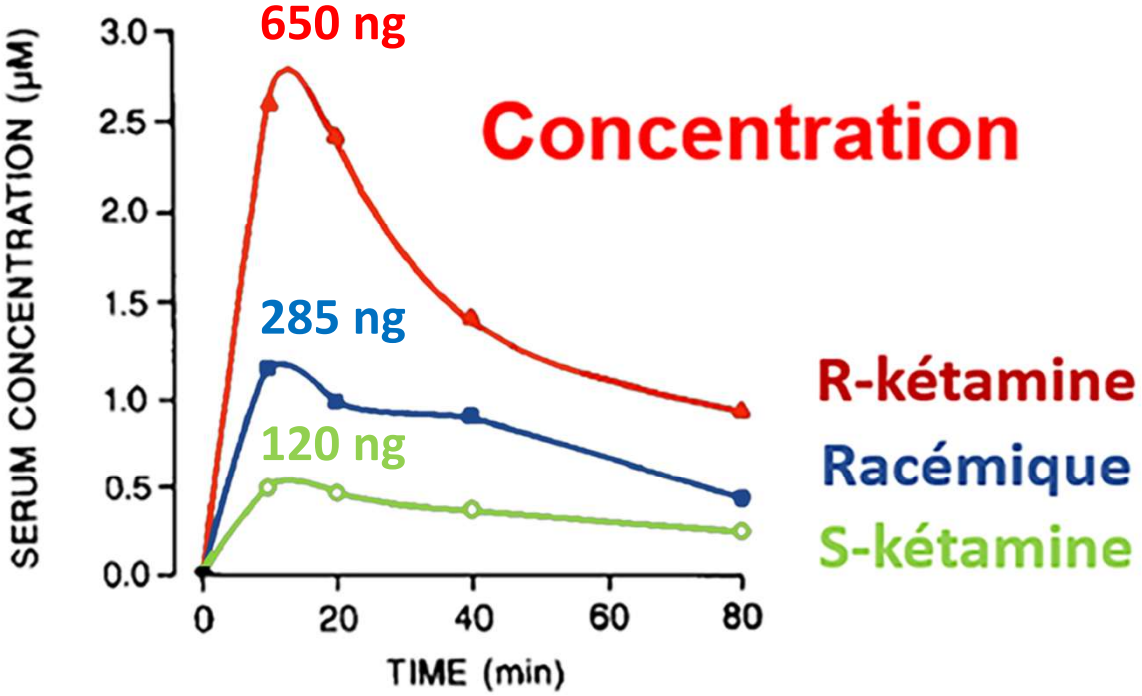
Pain, 61 (1995) 215–220

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

1 µMol = 237 ng



Douleur orofaciale



Concentration

R-kétamine

Racémique

S-kétamine

1997

Anesthesia with S(+)-ketamine

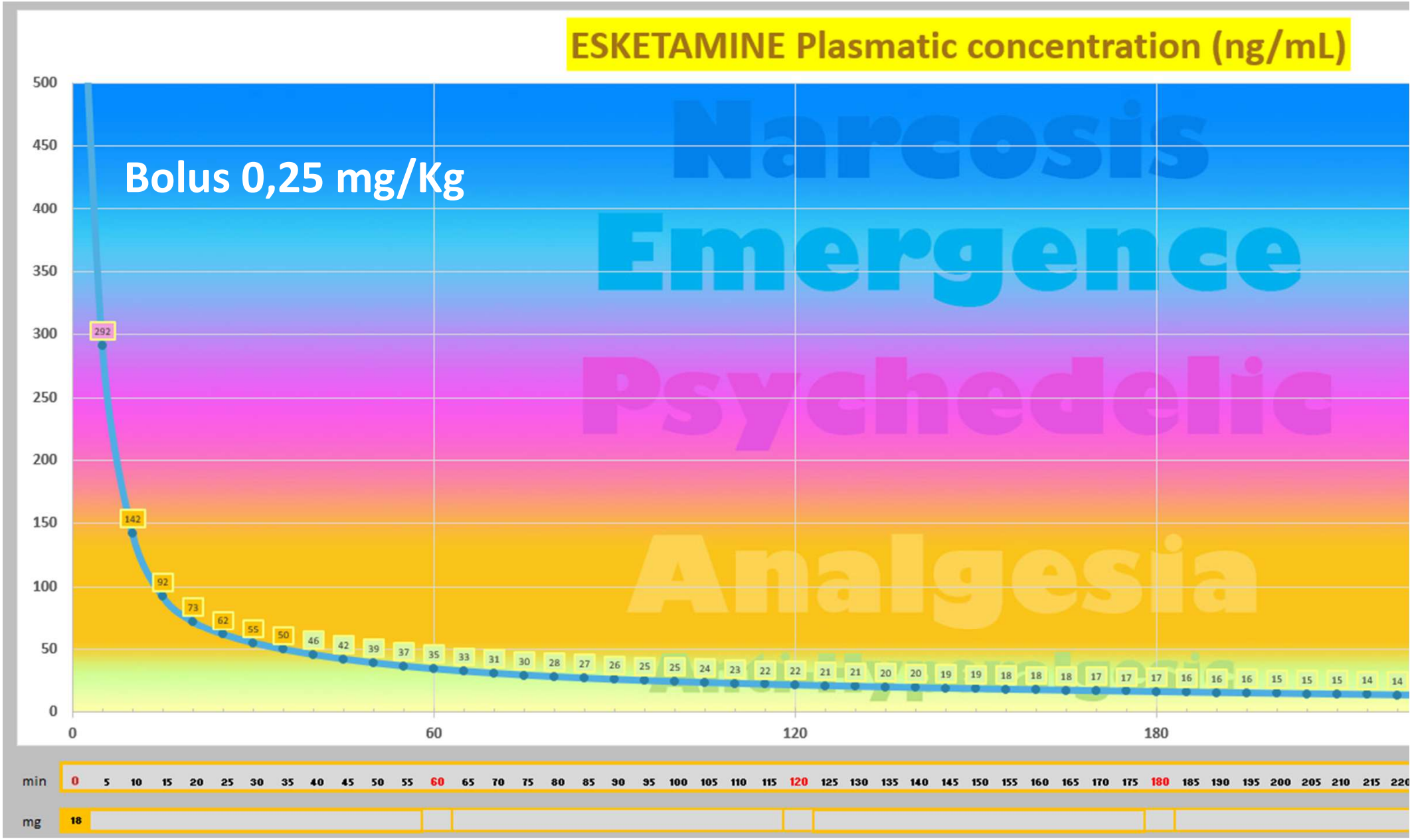
E. Pfenninger and S. Himmelseher[1]

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.

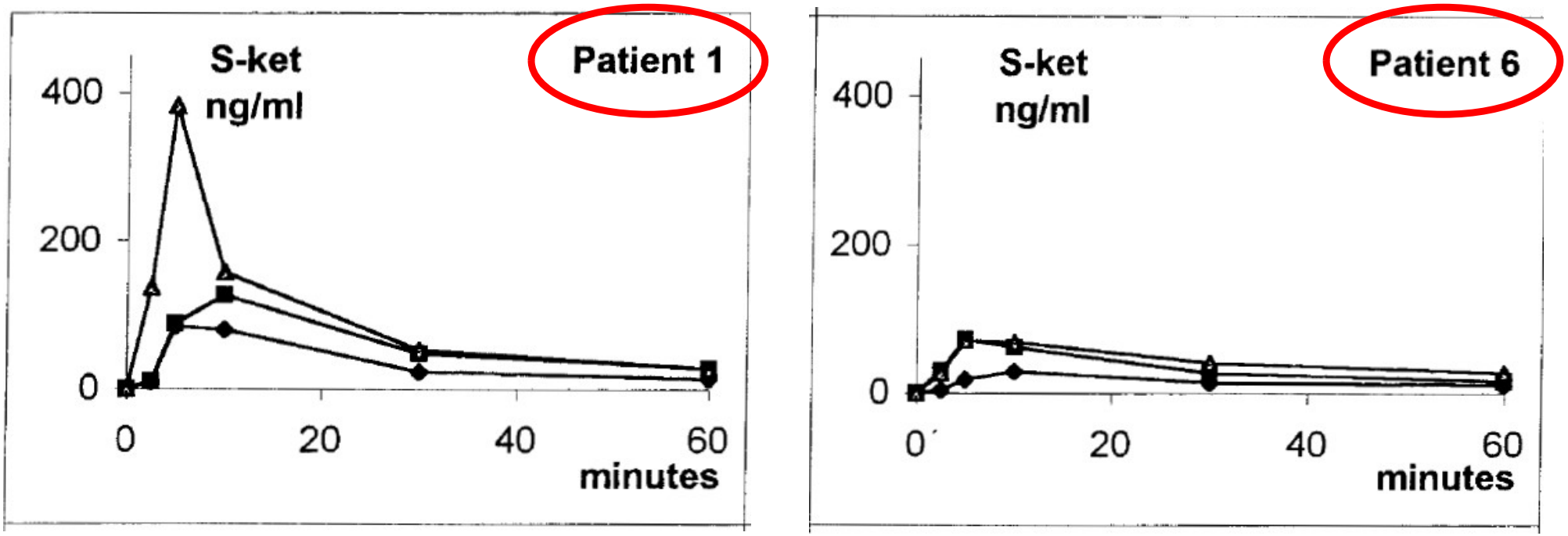
Relation conc/effet



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

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,
(−)ketamine (MK), 3 mg/kg,
randomized, double-blind
were administered intravenously to 60 healthy patients

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.

S+kétamine

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).

Moins de douleur

Moins de problèmes d'émergence et d'agitaton

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.

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

cognition

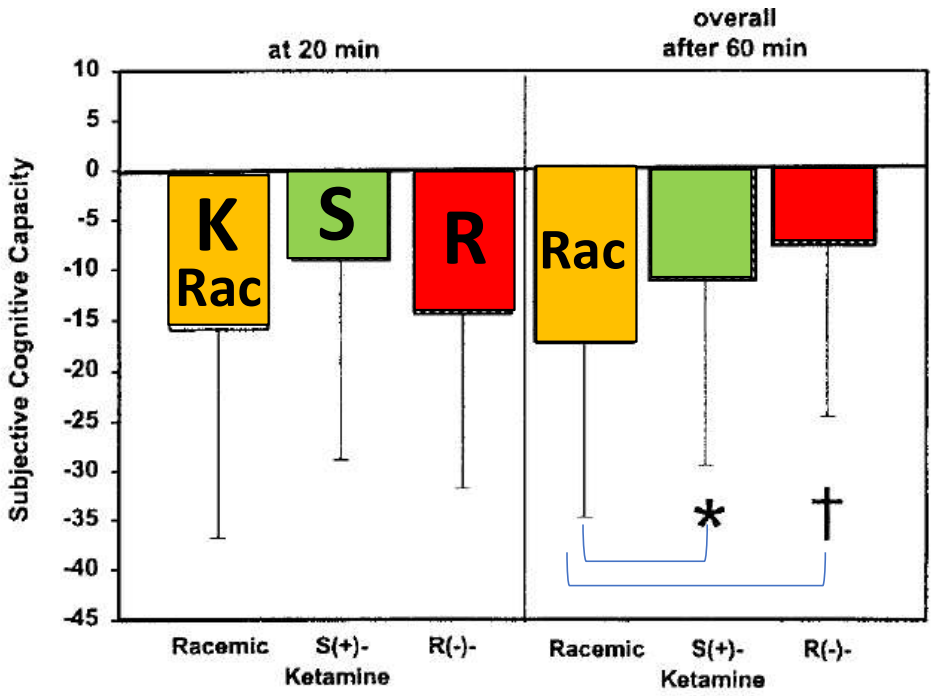


Fig. 3. Analysis of change of clustered rating scores for subjective cognitive capacity revealed less decline after *R*(−)- (*P* = 0.040) or *S*(+)-ketamine (*P* = 0.042) than after racemic ketamine for the overall period at 60 min. Bars show the mean ± SD. *Significant difference between racemic ketamine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

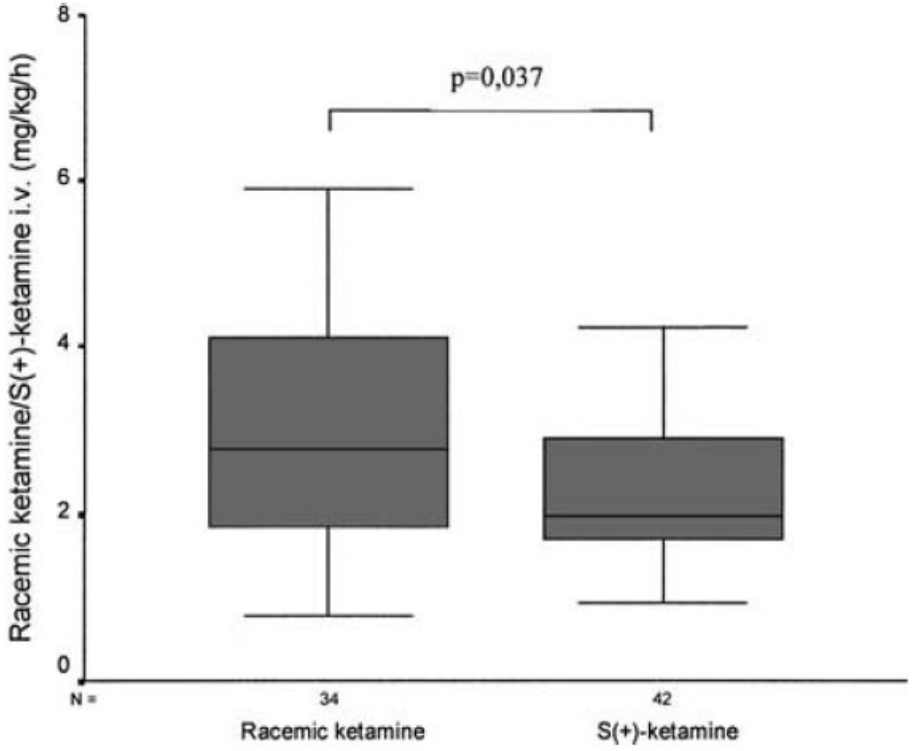
Davantage de problèmes cognitifs avec le racémique

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

mg/kg/h
(> 1000 ng/ml = **doses hypnotiques**)



Réveil plus rapide
Avec Eskétamine
96 vs 127 min (- 25%)

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.

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

Comment interpréter Ces différences ?

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**

BEHAVIORAL AND ELECTROENCEPHALOGRAPHIC EFFECTS OF ATROPINE AND RELATED COMPOUNDS

V. G. LONGO

Pharmacological Reviews June 1966, 18 (2) 965-996;

This review is concerned primarily with atropine and scopolamine; other anticholinergic compounds will be referred to when necessary. The effects observed in man will be reviewed in an attempt to set forth the essential and characteristic elements which make up the "central anticholinergic syndrome." In a separate

Physostigmine Antagonizes Ketamine

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

Anesth Analg 59:764–767 1980.

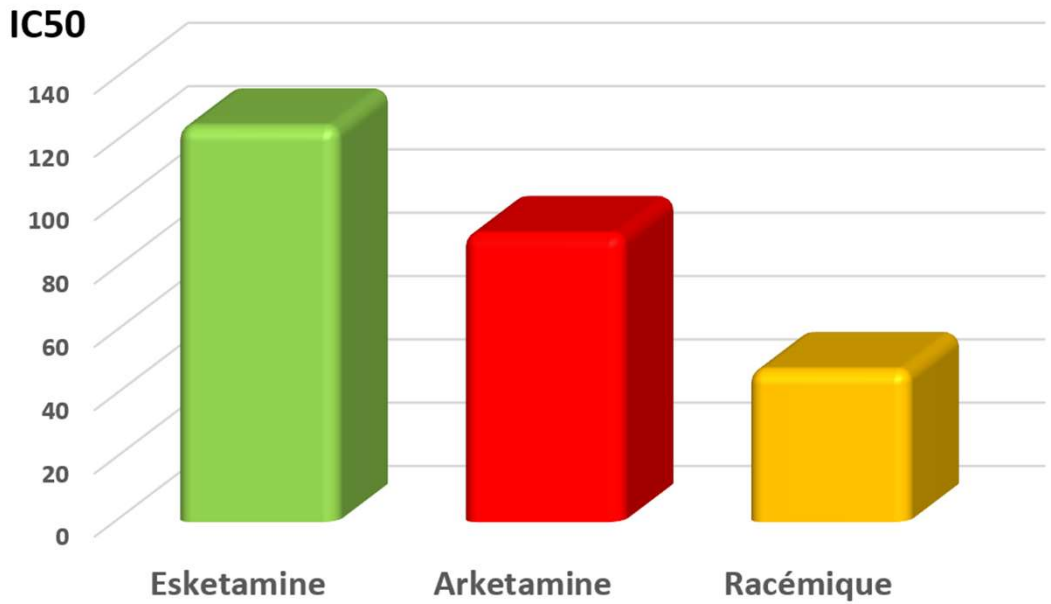
In a random cross-over double-blind trial, the effects of intravenous physostigmine salicylate (2.0 mg) and placebo were observed in seven healthy volunteers 10 minutes after the intravenous administration of 1.5 mg/kg of ketamine. Recovery time was significantly shorter after physostigmine than after 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.

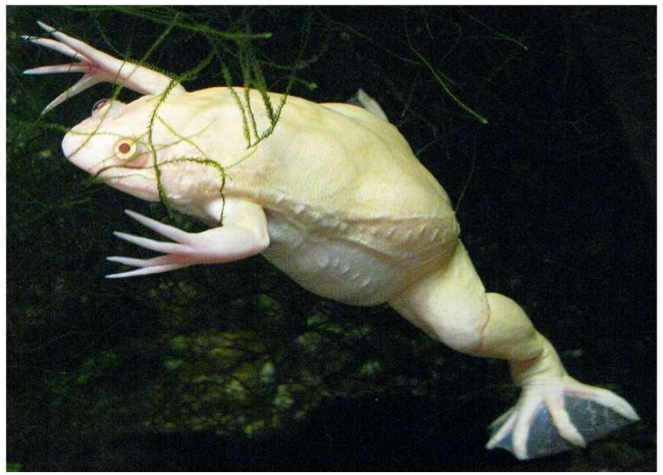
Synergistic Inhibition of Muscarinic Signaling by Ketamine Stereoisomers and the Preservative Benzethonium Chloride

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

Anesthesiology
1997; 86:1326-33

Inhibition des récepteurs muscariniques centraux





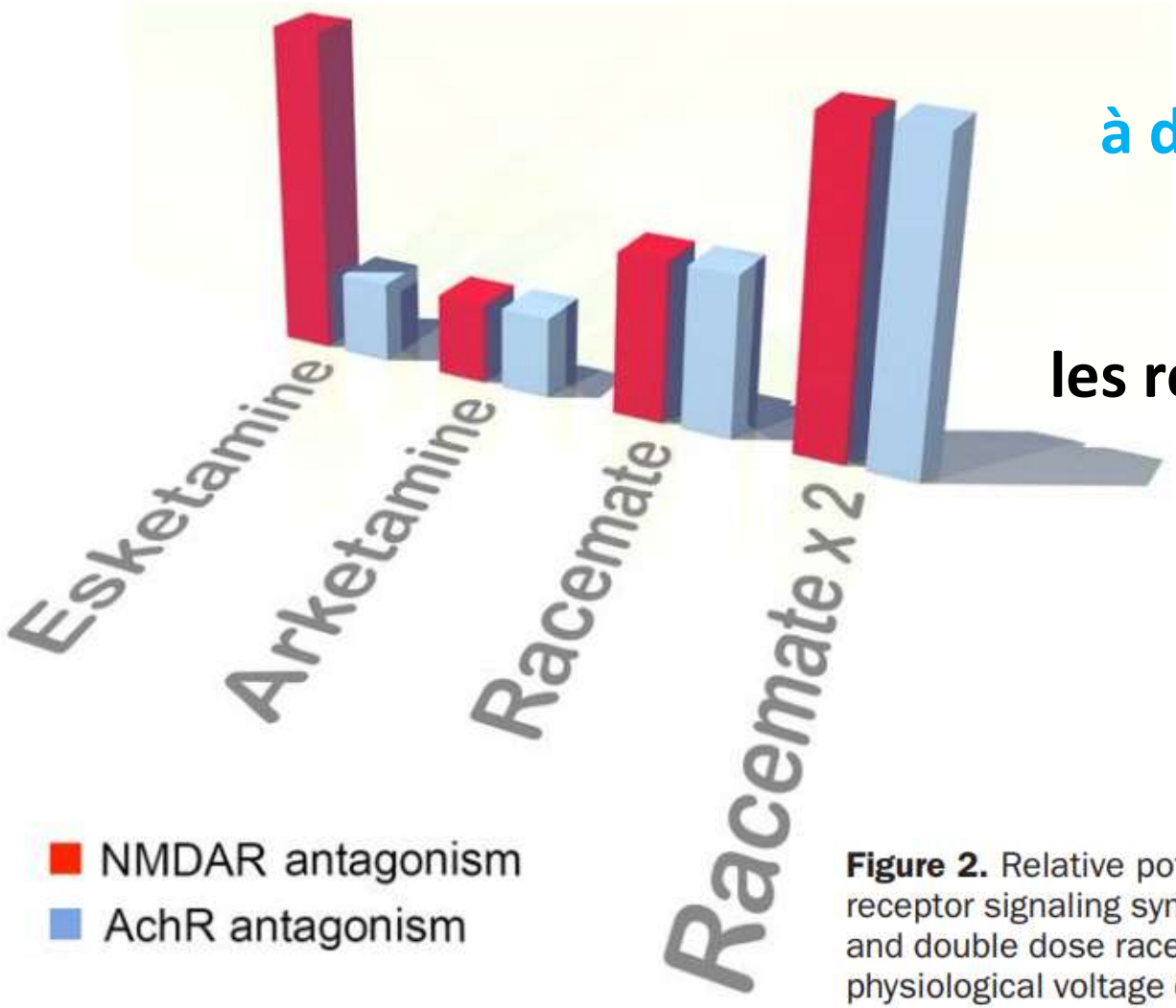
Methods: Rat m1 muscarinic acetylcholine receptors were expressed recombinantly in *Xenopus laevis* oocytes.

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.

Esketamine: Less Drowsiness, More Analgesia

Mion, Georges MD*; Himmelseher, Sabine MD†

Anesthesia & Analgesia 139(1):p 78-91, July 2024.

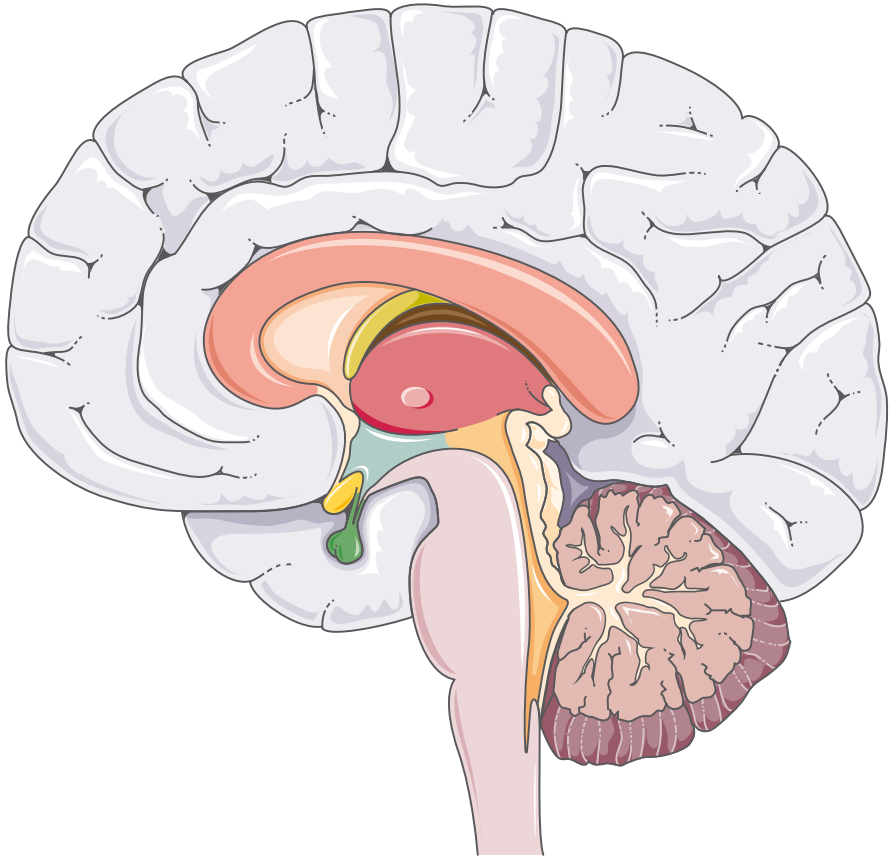


à doses équi-analgésiques
le racémique
Inhibe 4 fois plus
les récepteurs cholinergiques centraux
que l'eskétamine

Figure 2. Relative potency of antagonism for NMDA and muscarinic receptor signaling symbolized for esketamine, arketamine, racemate and double dose racemate. Bar graphs reflect the results of electrophysiological voltage clamped measurements gained in the xenopus laevis toad oocyte system with functional expression of rat receptors (based on data in Liu et al[14] and Durieux and Nietgen[15]). NMDA indicates N-methyl-D-aspartate.

2/3 1/3

GLU ← Excitation → ACh



(Inhibition → GABA)

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

British Journal of Anaesthesia, 125 (5): 750–761 (2020)

20 healthy volunteers

Three increasing i.v. doses of esketamine and racemic ketamine

Our analysis indicates major differences in S- and R-enantiomer pharmacokinetics, irrespective of their origin, with significant higher concentrations of R-ketamine, R-norketamine, and R-DHNK than the corresponding S-enantiomers (Fig 1). This corresponded with an up to 50% reduced elimination clearance of the R-compared with the S-enantiomers. It is generally accepted that S-enantiomer metabolism is favoured over R-enantiomer metabolism and is partly explained by the higher affinity of S-ketamine for the CYP3A4

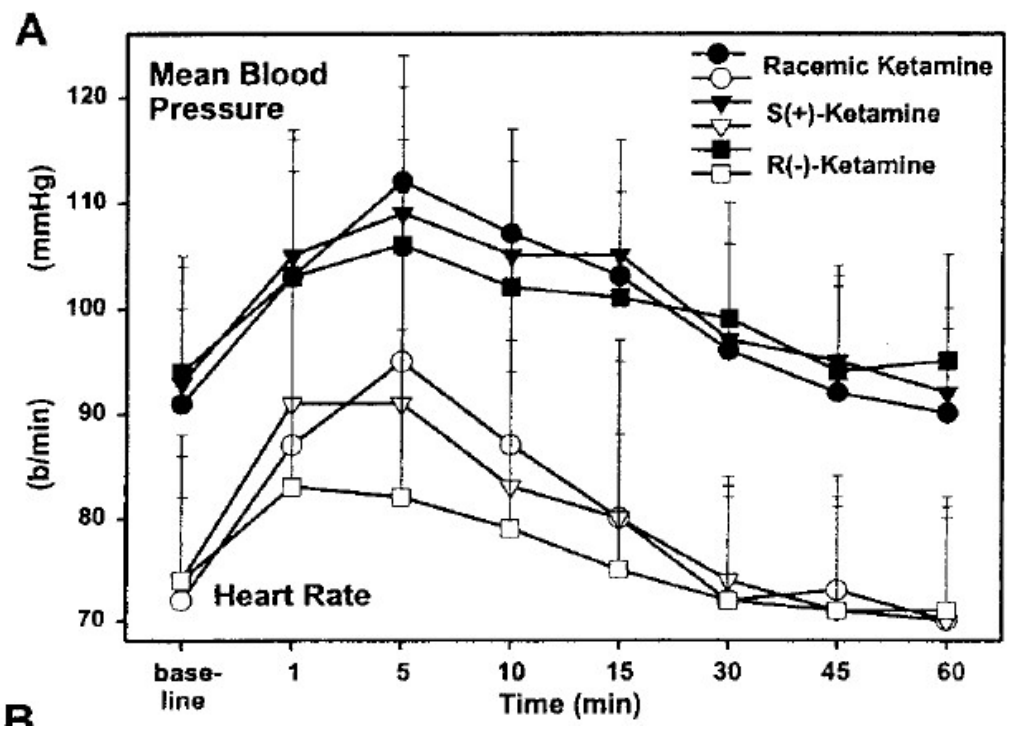
Effets cardiovasculaires

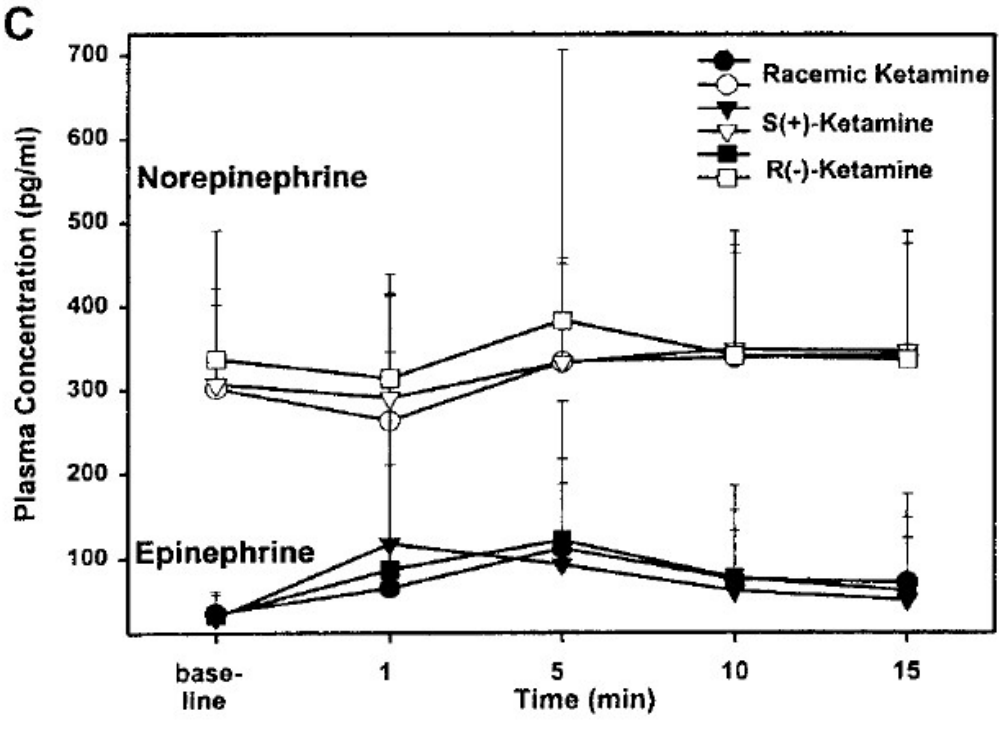
Cognitive Impairment after Small-dose Ketamine Isomers in Comparison to Equianalgesic Racemic Ketamine in Human Volunteers

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-**





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.)

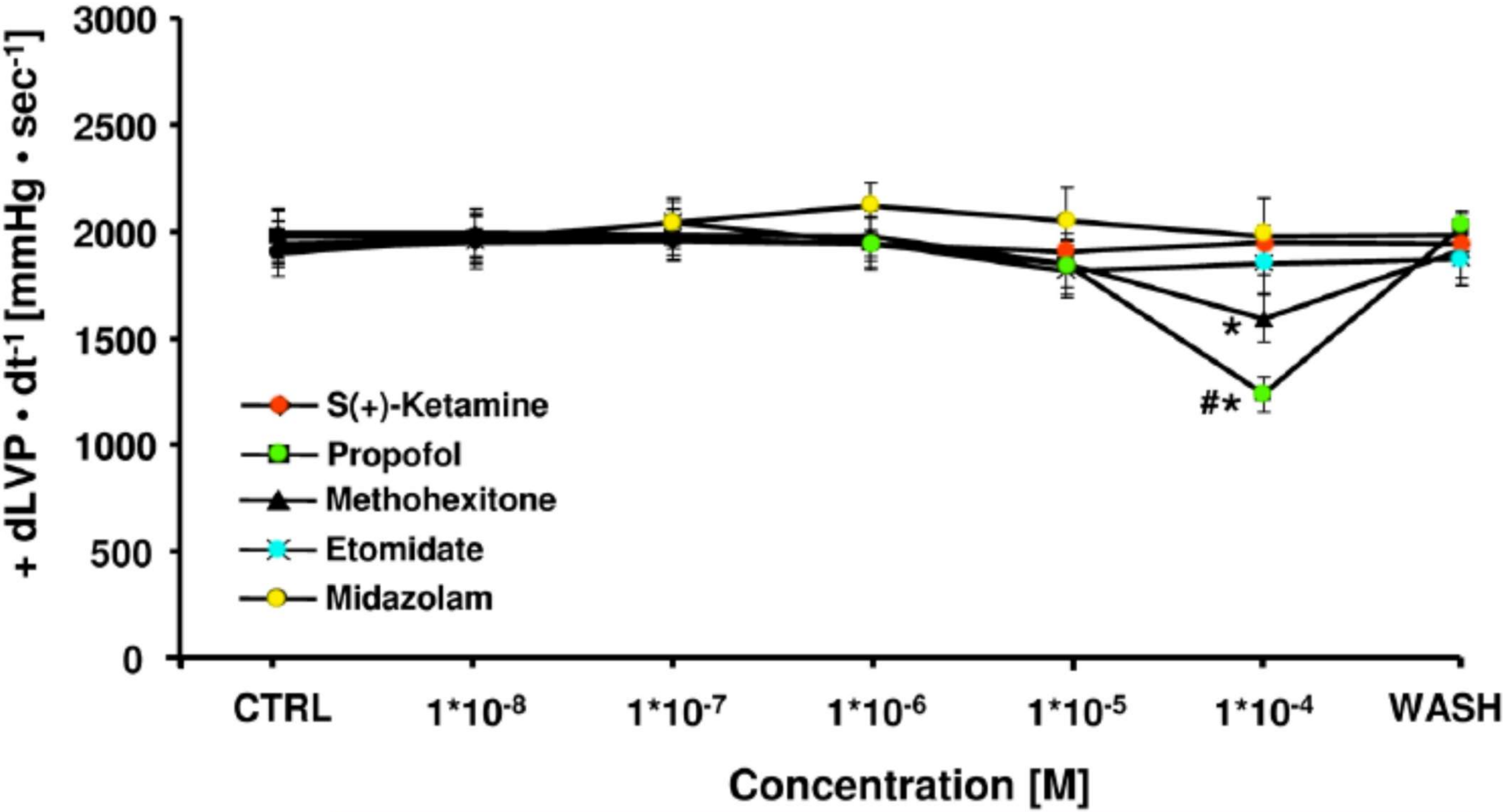
17 000 ng/L

170 000 ng/L

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



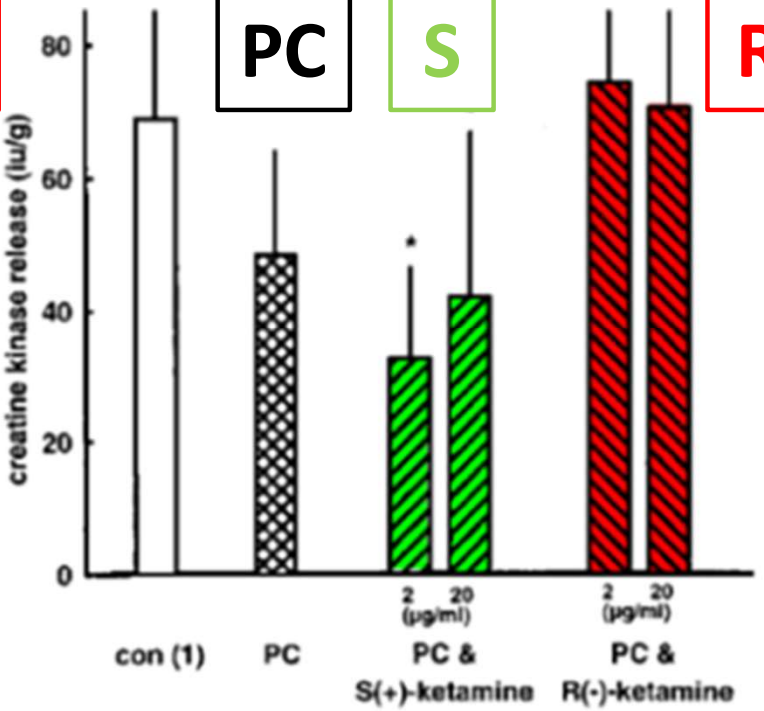
All drugs except for s(+)ketamine and midazolam decreased contractility.

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

CPK PC S R



Methods: Isolated rat hearts (n = 80) underwent 30 min of no-flow ischemia and 60 min of reperfusion. Two groups with eight hearts each underwent the protocol without intervention (control-1 and control-2), and, in eight hearts, preconditioning was elicited by two 5-min periods of ischemia before the 30 min ischemia. In the six treatment groups (each n = 8), ketamine, *R*(−)- or *S*(+)-ketamine were administered at concentrations of 2 or 20 µg/ml before preconditioning. Eight hearts received 20

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.

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-

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

Revising a Dogma: Ketamine for Patients with Neurological Injury?

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

(Anesth Analg 2005;101:524–34)

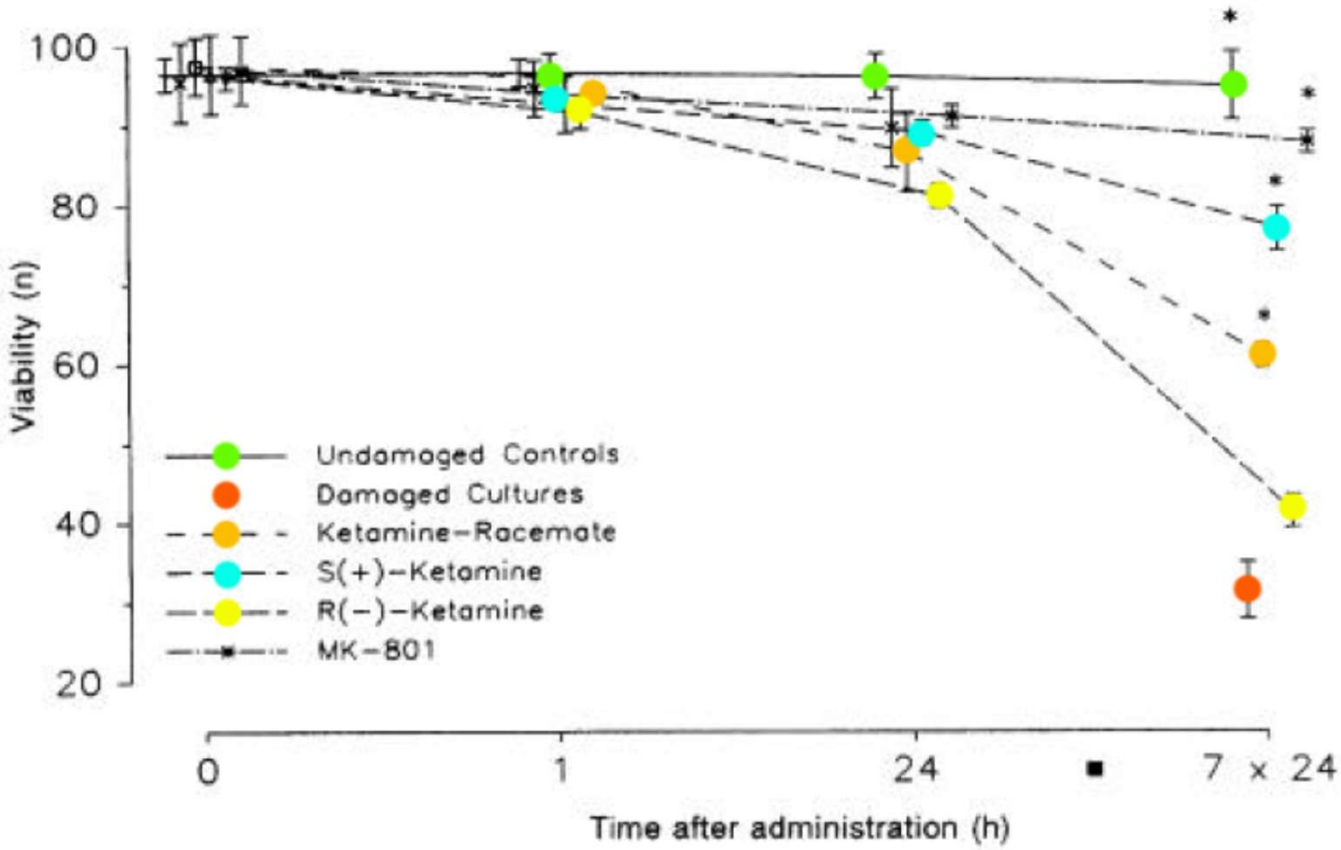
Severe brain trauma

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.

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)



Contrôle

Eskétamine

Racémique

Arkétamine

Glutamate

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

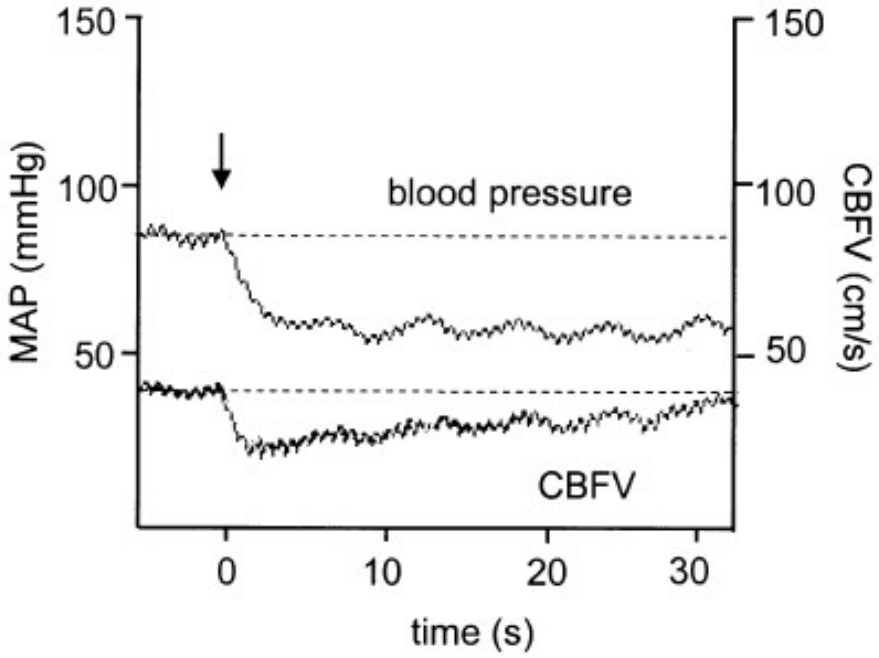
CAN J ANESTH 2001 / 48: 10 / pp 1034–1039

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

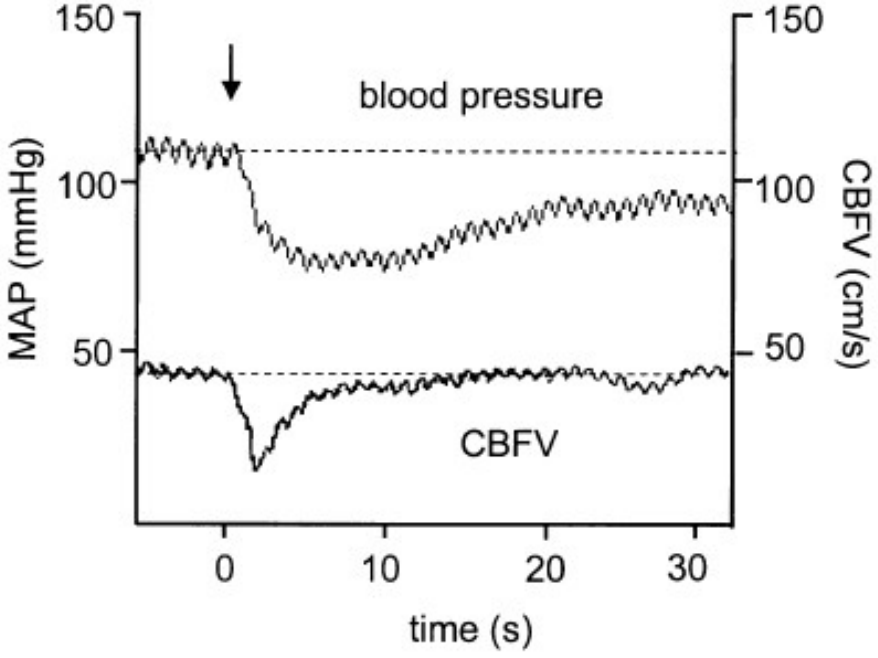
To assess dynamic cerebrovascular autoregulation the middle cerebral artery (MCA) blood flow velocity (CBFV) was measured by the transtemporal approach using a 2-MHz transcranial Doppler system (TCD,

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

sevoflurane



S(+)-ketamine/propofol



Expérience clinique

- **Analgésie** per et postopératoire
- **Sédation**
- **Récupération** postopératoire
  - Diminution **troubles cognitifs**
  - Prévention de la **dépression PO**
- **Douleur chronique**
- **En réanimation**

Analgésie

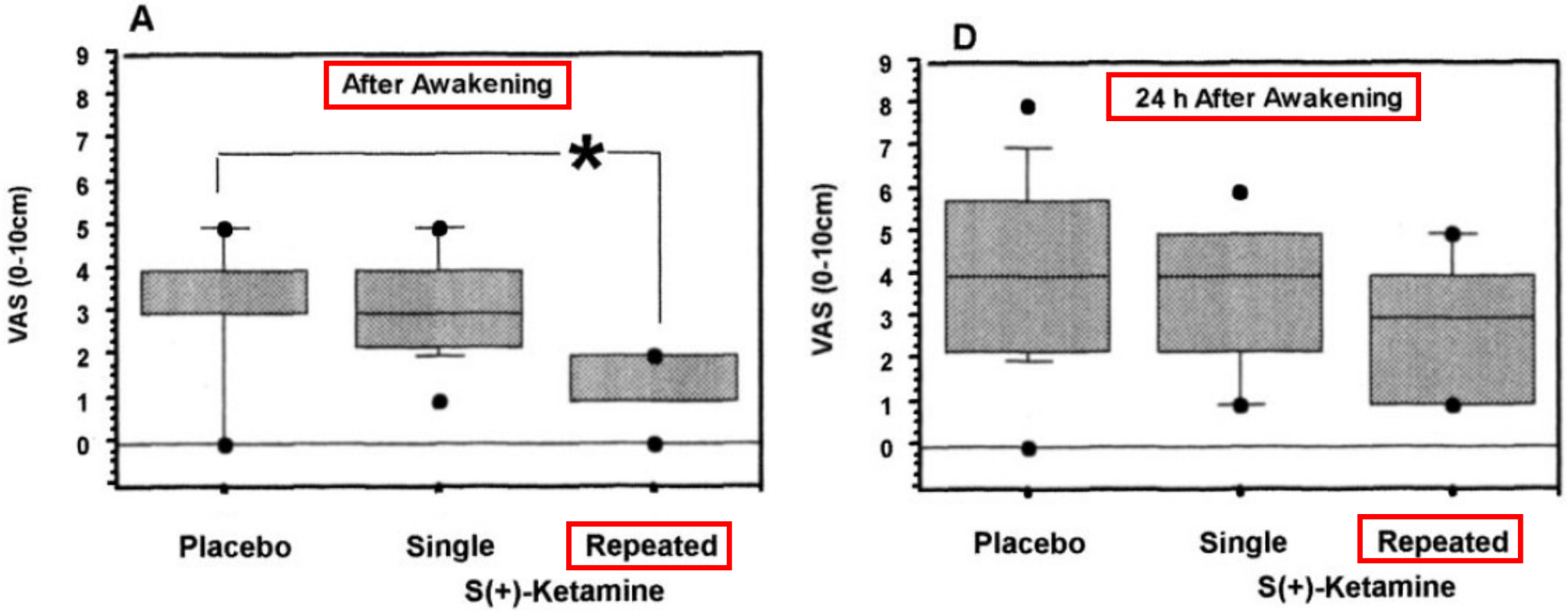
Improvement of Pain Treatment After Major Abdominal Surgery by Intravenous S(+)-Ketamine

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



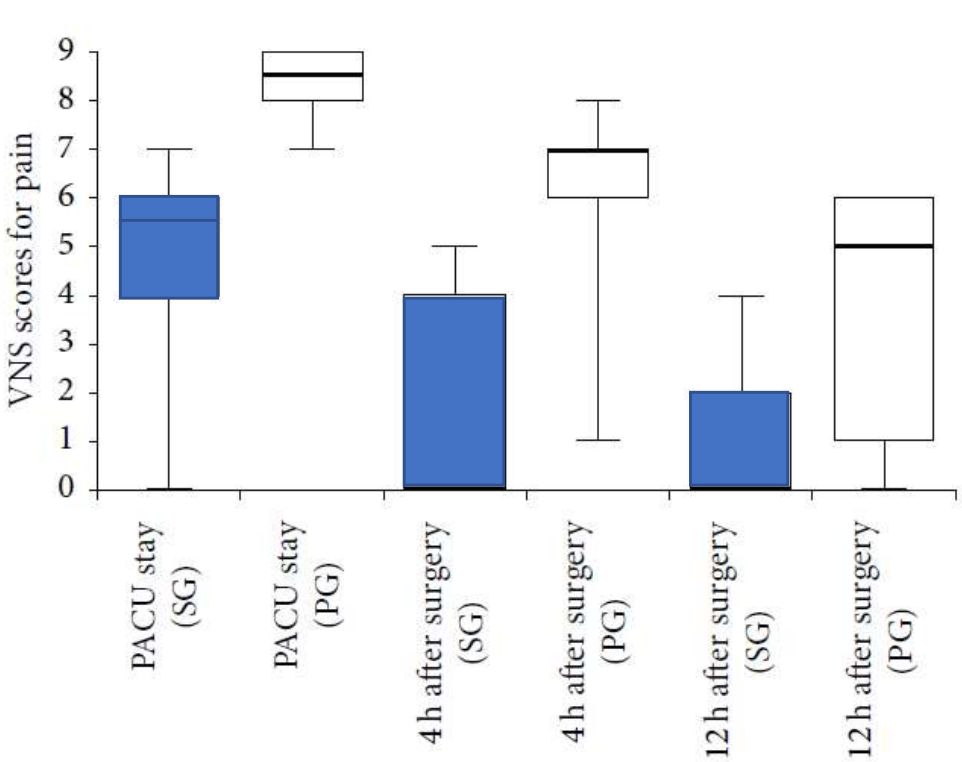
Efficacy of Continuous S(+)-Ketamine Infusion for Postoperative Pain Control: A Randomized Placebo-Controlled Trial

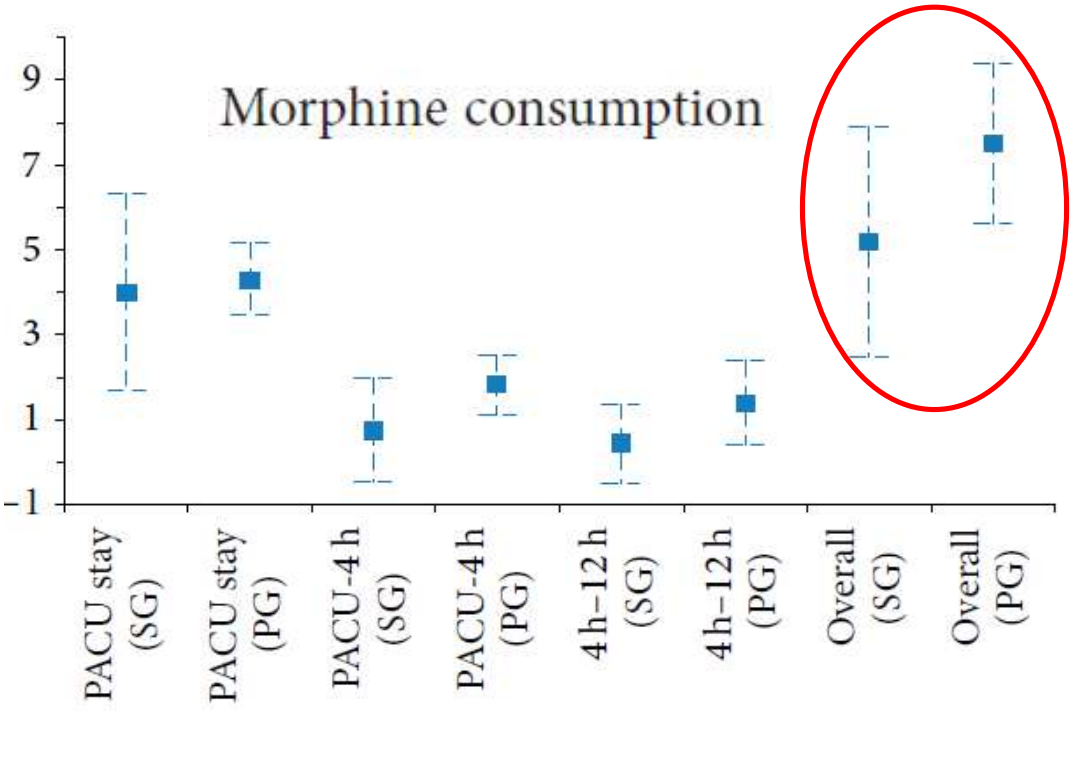
Péri opératoire

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





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

Per Op + PCA

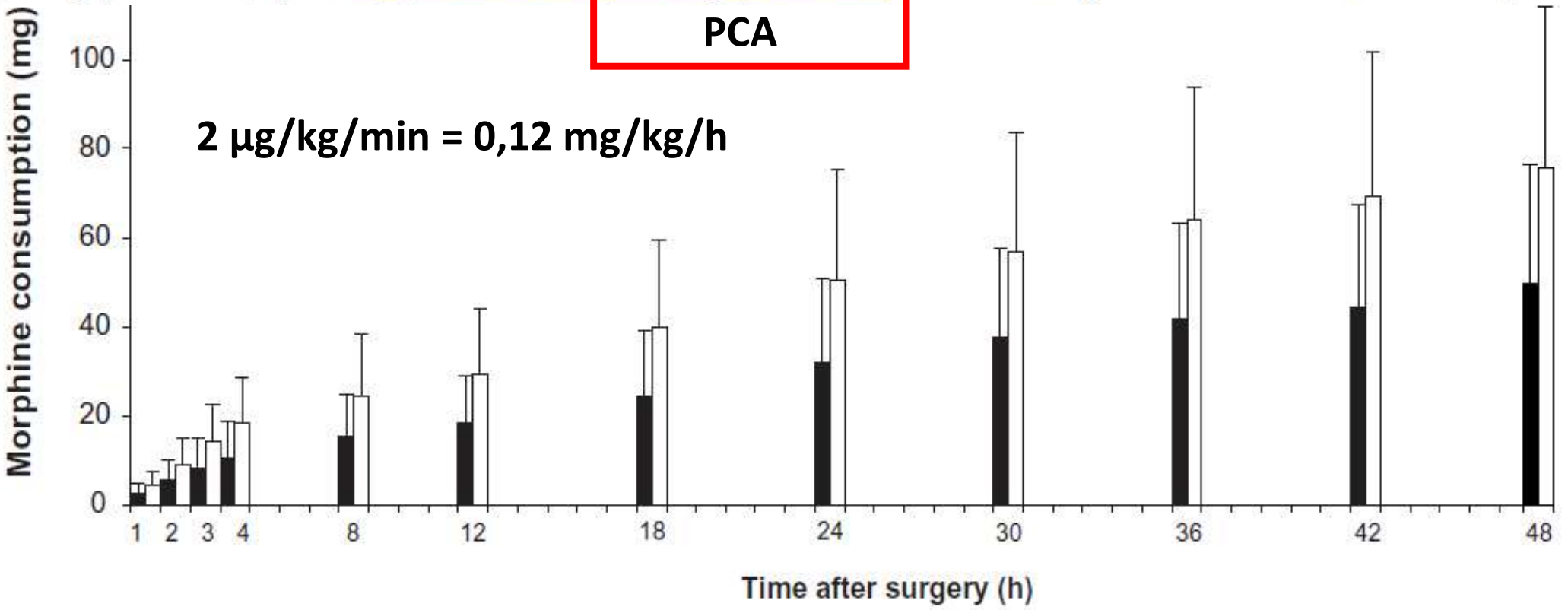
D. G. Snijdelaar,[1] H. B. Cornelisse,[2] R. L. Schmid[3] and J. Katz[4]

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

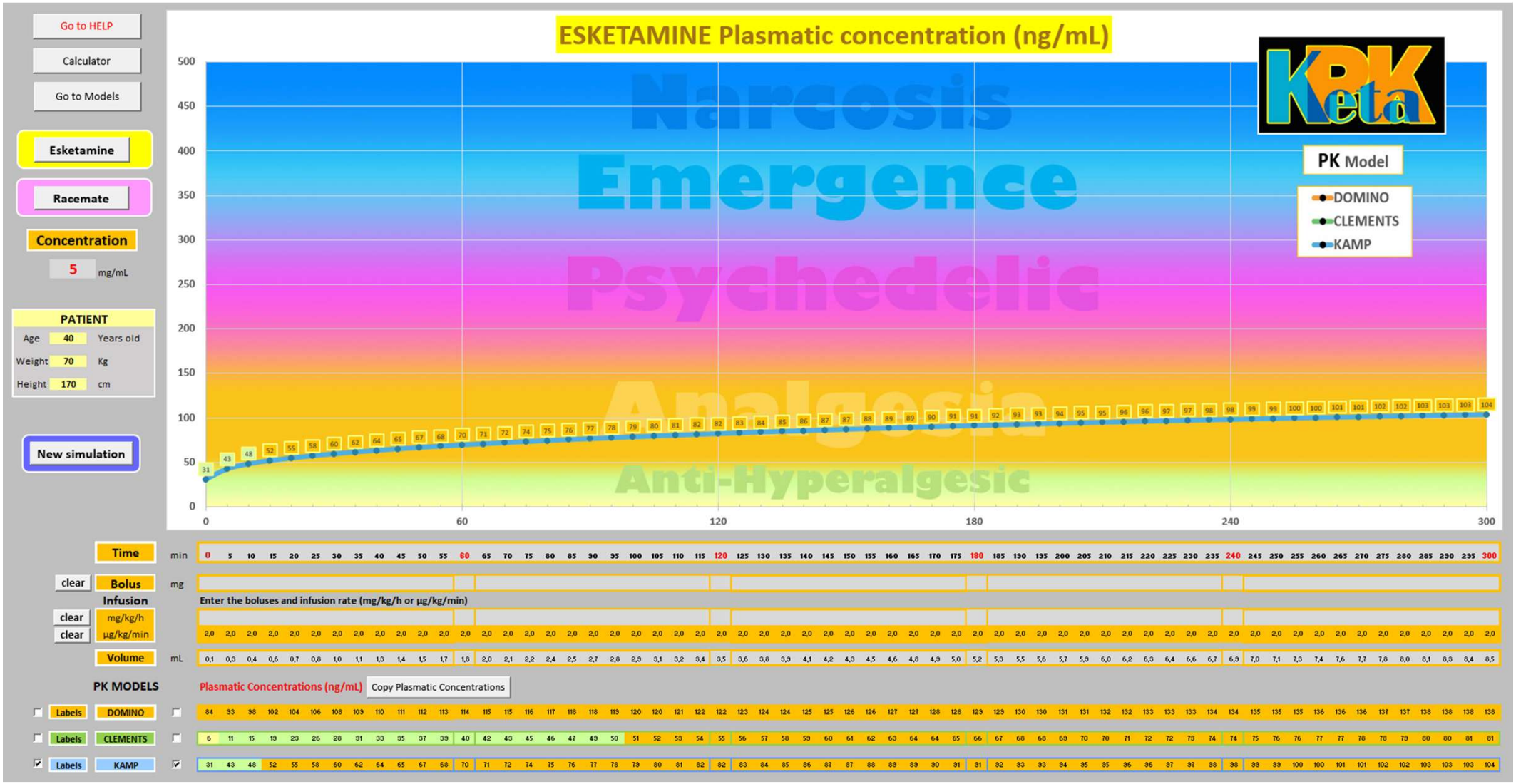
In a randomised, double-blind prospective study we compared the effects on postoperative pain and analgesic consumption of intra-operative s(+)-ketamine (100 $\mu g.kg^{-1}$ bolus and a continuous infusion of 2 $\mu g.kg^{-1}.min^{-1}$) followed by postoperative patient-controlled analgesia with morphine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

PCA

2 µg/kg/min = 0,12 mg/kg/h



2 µg/kg/min = 0,12 mg/kg/h



fourchette faible

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·kg^{-1}·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,

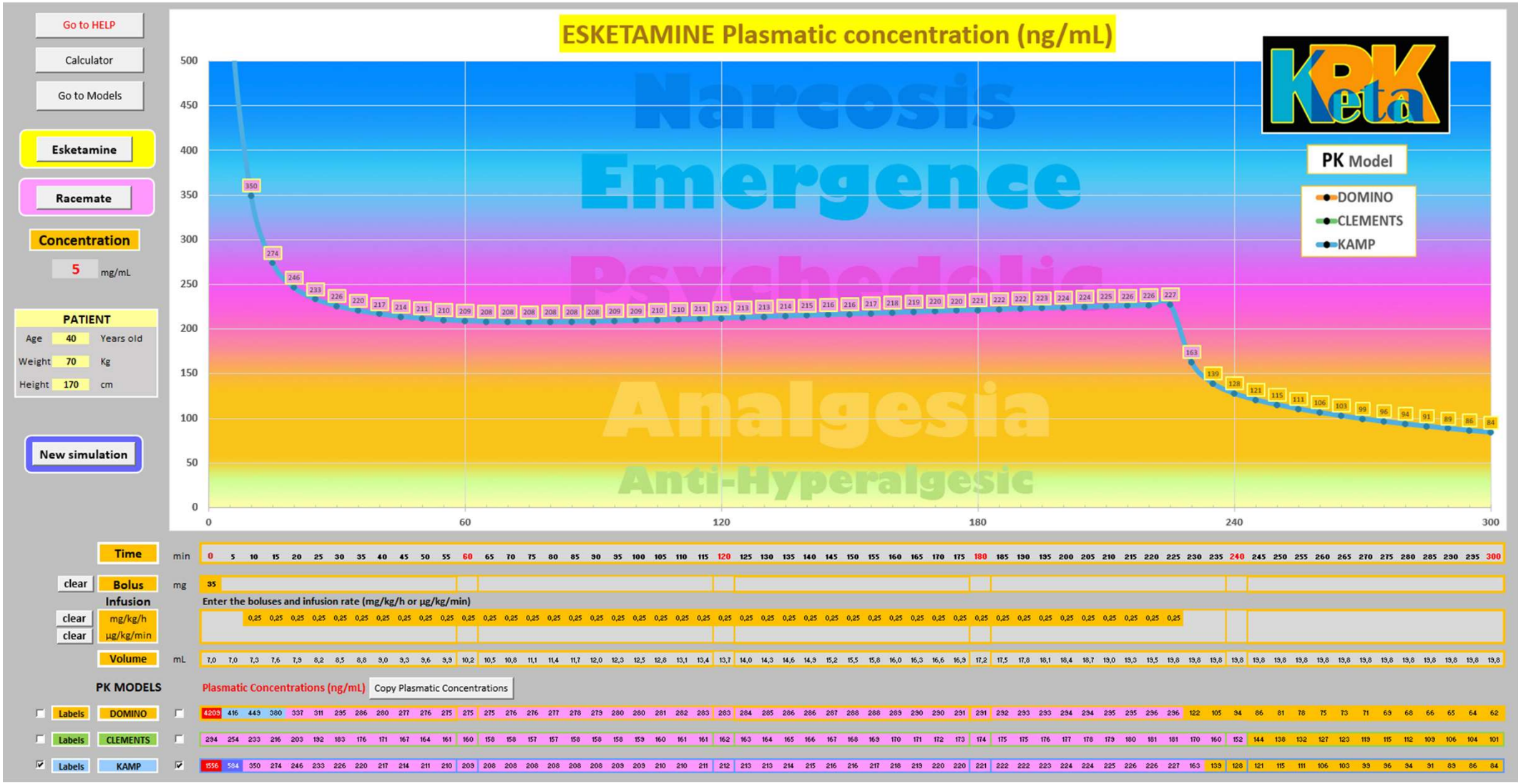
Péri opératoire

3.1. Morphine consumption

35%

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

Bolus 0,5 mg/kg + 0,25 mg/kg/h



Fourchette forte

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

Méta analyse 2021

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.

Pas de « magic bullet »

Effectiveness and safety of esketamine in laparoscopic surgery patients: a systematic review and meta-analysis of randomized controlled trials

Front. Pharmacol. 16:1663348.
doi: 10.3389/fphar.2025.1663348

Méta analyse 2025

Shuhui Wang[1], Wei Hao[2], Hao Fan[3], Jiasheng Wu[1] and Lifang Wu[1]*

Results: Fifteen studies involving 1,553 participants were included. Esketamine reduced postoperative VAS (SMD: −0.47; 95% CI [-0.89, −0.05]; P = 0.027) and NRS scores (SMD: −0.36; 95% CI [-0.70, −0.01]; P = 0.042). It also decreased AIS scores on the first (SMD: −0.55; 95% CI [-1.03, −0.07]; P = 0.026) and third days (SMD: −0.85; 95% CI [−1.42, −0.29]; P = 0.003), and ICFS-10 scores (first: SMD: −0.55; third: SMD: −0.62). Additionally, esketamine lowered remifentanil consumption (SMD: −0.58; P = 0.003) and infusion rate (SMD: −0.40; P = 0.001), while increasing plasma BDNF concentrations (SMD: 1.19; P = 0.044). Sensitivity analysis confirmed the stability of these results.

Conclusion: Esketamine alleviates postoperative pain, reduces remifentanil and opioid consumption, improves sleep quality and recovery, mitigates postoperative fatigue, and increases plasma BDNF concentrations in laparoscopic surgery patients. Nevertheless, this meta-analysis still has certain limitations, most notably the high heterogeneity of the studies incorporated and the limited geographical coverage of the research sites. Further studies are needed to confirm these findings and support its use in improving perioperative outcomes.

Amélioration de la sédation

The Role of Esketamine in Reducing Propofol-Related Adverse Events During Gastrointestinal Endoscopy: A Systematic Review and Meta-Analysis

Lin Ba [1], Na Xu [2], XiaoXiao Dong [3]

Méta-analyse 2025

Cureus 17(12): e99619.

Six RCTs (n = 1,199 patients) were included for qualitative synthesis. Three RCTs (n = 524) provided data for meta-analysis. The pooled analysis demonstrated that esketamine significantly reduced the risk of propofol-related adverse events (relative risk (RR) = 0.43, 95% confidence interval (CI): 0.23-0.82). Heterogeneity was high ($I^2 > 50\%$). Most studies had a low risk of bias, and sensitivity analysis confirmed the robustness of the findings. Esketamine appears to mitigate propofol-associated adverse events, including hypotension, bradycardia, and respiratory depression, during gastrointestinal endoscopy. Nevertheless, further well-designed, large-scale RCTs are needed to validate these findings and determine optimal dosing strategies.

Moins d'hypotension, de bradycardie,
et **de dépression respiratoire**
durant la sédation par propofol

Diminution des troubles cognitifs postopératoires

Role of Esketamine in Attenuating Neuroinflammation and Improving Postoperative Cognitive Function via Autophagy Activation Through PARP1 Targeting

Chendi ZHAO[1,2], Jiaxin LIU[1], Shuang ZHAO[1], Peng LIU[1], Zhao LI[1], Yongle LI[2], Rui DONG[3], Xiu-Li WANG[1]

Physiol. Res. 74: 871-884, 2025

2025

Exploratory laparotomy induced POCD and triggered neuroinflammation within the hippocampus of the mice. Treatment with esketamine alleviated POCD by inhibiting OvPARP1 expression and increasing SIRT1 levels, which promoted cellular autophagy and reduced neuroinflammation. Esketamine regulates the PARP1-SIRT1 pathway, thereby activating autophagy, reducing neuro-inflammation, and improving POCD.

L'eskétamine réduit la neuroinflammation périopératoire

PARP-1 = poly(ADP-ribose)-polymérase 1 (un détecteur moléculaire des cassures dans l'ADN)
SIRT1 est une désacétylase (protège des maladies cardiovasculaires et neurodégénératives)

ANESTHESIOLOGY®

Effect of S-Ketamine on Postoperative Delirium in Elderly Patients Undergoing Arthroplasty: A Randomized Controlled Trial

2026

Youzhuang Zhu, M.D., Ph.D., Wei Feng, M.D., Ph.D., Yang Zhao, M.D., Ph.D., Yaqi Han, M.S., Qinghan Kong, M.S., Dongyue Chai, M.S., Jia Liu, M.D., Ph.D., Peipei Shan, Ph.D., Shaoqi Tian, M.D., Ph.D., Lei Zhang, M.D., Ph.D.

ANESTHESIOLOGY 2026; 144:63–76

Methods: This study was conducted at a high-volume arthroplasty referral center where standardized, evidence-based perioperative protocols are implemented with high fidelity. This study included 372 elderly patients undergoing total hip or knee arthroplasty under neuraxial anesthesia. Patients were enrolled from November 2023 to October 2024, and in-person follow-up assessments were conducted from admission to 3 days after surgery. Patients were randomized to receive either S-ketamine (n = 186) or normal saline placebo (n = 186). The primary outcome was risk of POD within 3 days after surgery. Secondary outcomes were number of POD episodes, POD onset time and duration, POD severity, POD subtype, pain score (numeric rating scale), opioid consumption, number of patients requiring rescue analgesia, sleep quality, clinical outcomes, and harms.

The S-ketamine group received an intravenous infusion of 2.0 mg · ml^{-1} S-ketamine (Jiangsu Heng Rui Medicine Co. Ltd., China) in normal saline. The infusion was administered at a constant rate of 0.1 ml · (kg · h)$^{-1}$ [0.2 mg · (kg · h)$^{-1}$] for 1 h. The placebo group received an equivalent volume of normal saline, administered at the same infusion rate and

Results: Within 3 days after surgery, 15 patients in the S-ketamine group (8.06%) developed POD, compared to 38 patients (20.43%) in the placebo group (adjusted odds ratio, 0.29; 95% CI, 0.14 to 0.63; $P = 0.002$). On postoperative day 1, patients in the S-ketamine group experienced significantly less pain during exercise and physical therapy and had a lower incidence of rescue analgesia use compared to the placebo group. The incidence of hallucinations, dizziness, and nightmares was higher in the S-ketamine group than in the placebo group. The incidence of other complications was low in both groups, with no statistically significant differences.

Efficacy of intraoperative ketamine/esketamine in the prevention of postoperative delirium: a systematic review and meta-analysis

Méta-analyse 2025

Ther Adv Psychopharmacol

2025, Vol. 15: 1–16

Chengchuan Chen*, Na Zhou* and Jixin Hou

Eskétamine vs. racémique

Results: A total of 18 studies with a total of 1571 participants met eligibility criteria. A meta-analysis of all studies suggests that the intraoperative use of ketamine/esketamine may reduce the incidence of POD (RR = 0.71, 95% CI: 0.56, 0.90, $p < 0.01$). In the drug subgroup, esketamine demonstrated enhanced efficacy in preventing POD compared to ketamine (RR = 0.59, 95% CI: 0.38, 0.90, $p = 0.02$). In addition, subanesthetic doses of ketamine/esketamine (≤0.5 mg/kg) contributed to POD prevention (RR = 0.52, 95% CI: 0.34, 0.79, $p < 0.01$), whereas higher doses (>0.5 mg/kg) showed no statistically significant effect (RR = 0.89, 95% CI: 0.66, 1.21, $p = 0.46$). Further analysis revealed additional benefits of ketamine/esketamine in reducing POD incidence in cardiac surgery (RR = 0.46, 95% CI: 0.31, 0.68, $p < 0.01$), in the elderly (RR = 0.68, 95% CI: 0.52, 0.91, $p < 0.01$), and in the first 24 h post-surgery (RR = 0.52, 95% CI: 0.29, 0.94, $p = 0.03$).

Conclusion: Our findings suggest that perioperative administration of ketamine/esketamine had a protective effect against the incidence of POD, with esketamine demonstrating superior efficacy compared to ketamine. The treatment effect exhibited a dose-response relationship, with subanesthetic doses showing greater efficacy. Furthermore, ketamine/esketamine may offer additional benefits for patients with specific risk factors.

Impact of perioperative esketamine on the perioperative neurocognitive dysfunction: a systematic review and meta-analysis of randomised controlled studies

Méta-analyse 2025

Su X, *et al. BMJ Open* 2025;**15**:e095695.

Xuesen Su,[1] Lu Chen,[2] Yanan Zhao,[3] Chao Li,[1] Shufang Liu,[1,4] Zixuan Wang,[1,5] Jiayu Zhu,[1,6] Xin Yuan,[7] Yihe Tian,[8] Shouyuan Tian [1]

Results 10 RCTs were included in our meta-analysis, involving 854 surgical patients. Perioperative esketamine was associated with a reduced risk of postoperative delirium (POD) (relative risk (RR): 0.46, 95% CI: 0.30 to 0.71, p<0.001) and delayed neurocognitive recovery (dNCR) (RR: 0.41, 95% CI: 0.21 to 0.78, p<0.001). However, no statistically significant difference was found in the risk of postoperative neurocognitive disorder (post-NCD) at 3 months postsurgery between the esketamine and control groups (RR: 0.57, 95% CI: 0.19 to 1.73, p=0.40). Additionally, pain severity was reduced on postoperative day 1, with no difference in the risk of adverse events or length of hospital stay.

Récupération postopératoire

The impact of perioperative ketamine or esketamine on the subjective quality of recovery after surgery: a meta-analysis of randomised controlled trials

Kuo-Chuan Hung[1,†], Chia-Li Kao[2], Chun-Ning Ho[1,3,†], Chung-Hsi Hsing[1,4], Ying-Jen Chang[1], Li-Kai Wang[1], Shu-Wei Liao[1] and I-Wen Chen[5,*]

British Journal of Anaesthesia, 132 (6): 1293–1303 (2024)

Méta-analyse 2024

Results: The analysis included 18 RCTs (1554 participants; ketamine: seven trials, esketamine: 11 trials), of which 15 were conducted in China. Ketamine/esketamine improved the QoR scores on PODs 1 and 2 compared with the control (standardised mean difference [SMD]: 0.63, $P<0.0001$ for POD 1; SMD: 0.56, $P=0.04$ for POD 2), without beneficial effect on POD 3. Subgroup analyses revealed significant differences in QoR scores on POD 1 by regimen (SMD: esketamine 1.14, ketamine 0.01) and country (SMD: China 0.82, other countries −0.21). The emotional domain of QoR was improved from PODs 1 to 3, whereas the other domains were only improved on POD 1. Lower postoperative anxiety (SMD: −0.48, $P=0.003$) and depression (SMD: −0.72, $P=0.001$) scores were also observed with ketamine/esketamine use. Furthermore, pain severity was reduced on PODs 1 and 2, with no difference in the risk of adverse events or length of stay.

Conclusions: This meta-analysis demonstrated that ketamine/esketamine use in the perioperative period is associated with improved early subjective QoR, pain severity, and psychological symptoms without an increase in the likelihood of adverse events.

QoR 15 et 40 explorent cinq dimensions de la santé du patient :
douleur, confort physique, indépendance physique,
accompagnement psychologique et état émotionnel.

Effects of perioperative intravenous esketamine on postoperative recovery quality in adult patients: a systematic review and meta-analysis

Peer 2025;J13:e19977

Méta-analyse 2025

Zibang He, Jin Wu, Chun Yang and Peng Jiang

Results. Nineteen studies involving 1,967 patients were included. No significant differences were observed between the esketamine and control groups in PACU stay time (MD = 0.99, 95% confidence interval (CI) [−2.31–4.30], $P = 0.56$) or extubation time (MD = 1.30, 95% CI [−1.10–3.17], $P = 0.34$). However, the esketamine group showed significantly higher postoperative QoR-40 scores (MD = 9.40, 95% CI [6.12–12.69], $P < 0.00001$) and QoR-15 scores (MD = 7.43, 95% CI [3.97–10.88], $P < 0.0001$) compared to the control group.

Conclusion. Perioperative intravenous esketamine does not significantly affect PACU stay time, extubation time, or the incidence of postoperative mental side effects. However, it can reduce pain within 24 hours after surgery, improve sleep quality, decrease the incidence of PONV, and enhance postoperative recovery as reflected by higher QoR scores.

Efficacy and safety of intraoperative esketamine for postoperative sleep quality: a systematic review and meta-analysis of RCTs

Min Zeng[1] · Mingliang Yi[1] · Hong Yin[1] · Tingting Zheng[1] · Ying Peng[1]

Méta-analyse 2025

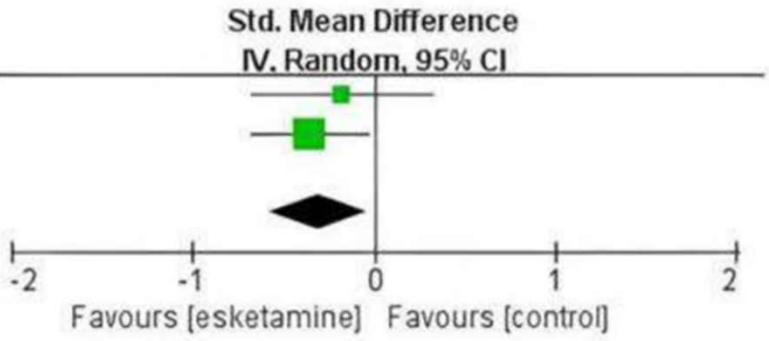
Sleep and Biological Rhythms (2025) 23:373–383

To evaluate the efficacy and safety of intraoperative esketamine in improving postoperative sleep quality based on evidence from randomized controlled trials (RCTs). A systematic search was conducted in the Cochrane Central Register of Controlled Trials (CENTRAL), Medline (via Ovid), and EMBASE. Eligible studies were RCTs comparing the effects of esketamine versus placebo on postoperative sleep quality in surgical patients. Statistical analyses were performed using Cochrane Review Manager version 5.4.1. A total of 10 RCTs comprising 1,287 patients were included. Esketamine significantly improved postoperative sleep quality compared to placebo on postoperative day (POD) 1 (SMD = −0.52, 95% CI [−0.69, −0.34], $P < 0.00001$, $I^2 = 61\%$), POD 2 (SMD = −0.60, 95% CI [−1.16, −0.03], $P = 0.04$, $I^2 = 77\%$), POD 3 (SMD = −0.44, 95% CI [−0.71, −0.18], $P = 0.001$, $I^2 = 76\%$), and POD 7 (SMD = −0.31, 95% CI [−0.58, −0.04], $P = 0.03$, $I^2 = 0\%$). While the incidence of adverse events did not differ significantly between groups, elevated odds ratios indicated a potential trend toward a higher incidence with esketamine. Intraoperative esketamine may improve postoperative sleep quality. However, it is not yet possible to conclude whether this agent is suitable for clinical use in improving sleep targeting postoperative patients. Further high-quality RCTs are needed to confirm efficacy and evaluate long-term safety.

(c) POD 7

Study or Subgroup	esketamine Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Lei Sun 2023	5.84	1.35	32	6.07	1.17	30	29.1%	-0.18 [-0.68, 0.32]
Xiaoyan Ma 2024	8.65	0.75	78	9	1.15	75	70.9%	-0.36 [-0.68, -0.04]
Total (95% CI)			**110**			**105**	**100.0%**	**-0.31 [-0.58, -0.04]**

Heterogeneity: Tau² = 0.00; Chi² = 0.36, df = 1 (P = 0.55); I² = 0%
Test for overall effect: Z = 2.24 (P = 0.03)



Effectiveness of ketamine/esketamine in alleviating postoperative fatigue: a systematic review

Qijing Liu[1] · Ying Liu[1] · Qian Fu[1] · Boxiong Gao[1] · Chengying Ji[1] · Jiayi Xie[1] · Bokang Yang[1] · Jinxiang Xie[1] · Abdulrahman Khaled Alwesabi[1] · Yatao Liu[2]

International Journal of Clinical Pharmacy Published online: 12 November 2025

Revue Syst 2025

Results In total, 556 studies were identified. Nine studies (n = 1606) were included in this review, among which seven were randomized controlled trials (RCTs) and two were observational studies. Four RCTs had low risk of bias, while the remaining three had some concerns. The two cohort studies were of moderate quality. The included studies encompassed various surgical procedures: colorectal cancer resection (n = 2), gastric surgery (n = 1), hysterectomy (n = 1), breast surgery (n = 2), orthopedic surgery (n = 1), and gastrointestinal endoscopy (n = 2). The outcomes varied according to the type of surgery. In studies of major abdominal surgeries, ketamine/esketamine has demonstrated certain potential in improving POF, but the certainty of evidence was graded as low. In contrast, no significant benefits were observed in breast or orthopedic surgeries. In the two studies on gastrointestinal endoscopy, the results were inconsistent.

Conclusion Current evidence suggests that ketamine/esketamine may be effective in alleviating POF, particularly in major abdominal surgeries. These findings should be interpreted cautiously due to the heterogeneity in study designs, variations in fatigue assessment tools and time, and the limited sample sizes of the included studies. Future high-quality RCTs are needed to confirm these observations and establish the optimal dosing regimens.

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Prévention de la dépression postopératoire

Efficacy of perioperative esketamine on postoperative depression: a systematic review and meta-analysis

Hao-Yan Li, Wen-Jing Xu, Ya-Mei Wang, Shuang Xie* and Huan-Liang Wang*

Front. Psychiatry 16:1476449.
doi: 10.3389/fpsyt.2025.1476449

ANESTHESIOLOGY

Association between Preoperative Depression and Length of Stay after Major Surgery: A Systematic Review and Meta-analysis

Luka Kremic, M.D., Arzina Jaffer, M.D., Krisha Patel, B.M.Sc., Sandra Lee, M.D., Yuanxin Xue, M.D., Julian F. Daza, M.D., Jessica Petricca, M.D., Maggie Xiao, M.D., Bianca Pivetta, M.D., Karim S. Ladha, M.D., M.Sc., Duminda N. Wijeysundera, M.D., Ph.D., Calvin Diep, M.D.

Anesthesiology 2025; 143:929–43

Méta-analyse 2025

Results: We included a total of 8 randomized controlled trials involving 1724 patients who met the criteria. The meta-analysis revealed that esketamine treatment, compared with control groups, significantly reduced POD. Improvements were observed at 1 week (RD -0.09, 95% CI [-0.13, -0.05], P < 0.0001, I^2=84%), 2 weeks (RD -0.08, 95% CI [-0.13, -0.03], P < 0.00001, I^2=97%), and long-term follow-up (RD -0.06, 95% CI [-0.10, -0.02], P=0.0002, I^2=79%).

Efficacité = dose-dépendante +++

Ketamine Analgesia: Not All Patients or Surgeries Seem to Be Equal

anesthesia-analgesia.
June 2021 • Volume 132

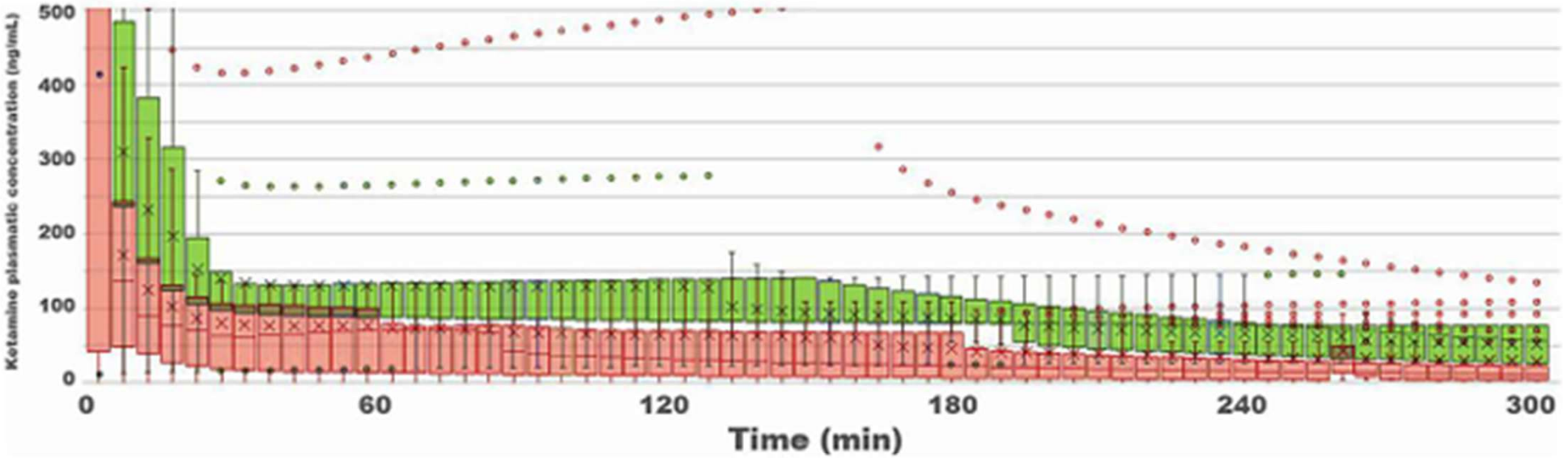


Figure. Ketamine plasmatic concentrations have been simulated for 5 h (intraoperative and early postoperative periods) according to the Domino model for each study administration scheme. The median, first and third quarters, and extreme values are represented as box-plots. The crosses represent the weighed means taking into account each study size. A total of 226 patients received ketamine in the 8 positive studies (De Kock et al,[3] Suzuki et al,[5] Perrin and Purcell,[6] Remérand et al,[7] Aveline et al,[8] Nielsen et al,[9] Liu et al,[10] Kang et al[11]) and 694 in the 16 negative studies (Katz et al,[12] Hayes et al,[13] Dualé et al,[14] Ryu et al,[15] Joseph et al,[16] Mendola et al,[17] Wilson et al,[18] Crousier et al,[19] Sveticic et al,[20] Dullenkopf et al,[21] Sen et al,[22] Spreng et al,[23] Bilgen et al,[24] Peyton et al,[25] Shanthanna et al,[26] Czarnetzki et al[27]). The concentrations provided in the positive studies (green) are significantly higher ($P < .001$) than those provided in the negative studies (pink), but extreme values show that some studies escape the average behavior.

Proposition de protocole en analgésie préventive

- **Bolus initial** :
  immédiatement (15 sec) avant le propofol (supprime la douleur à l'injection) ou avant l'incision

  IVL **0,2 à 0,35 mg/Kg**

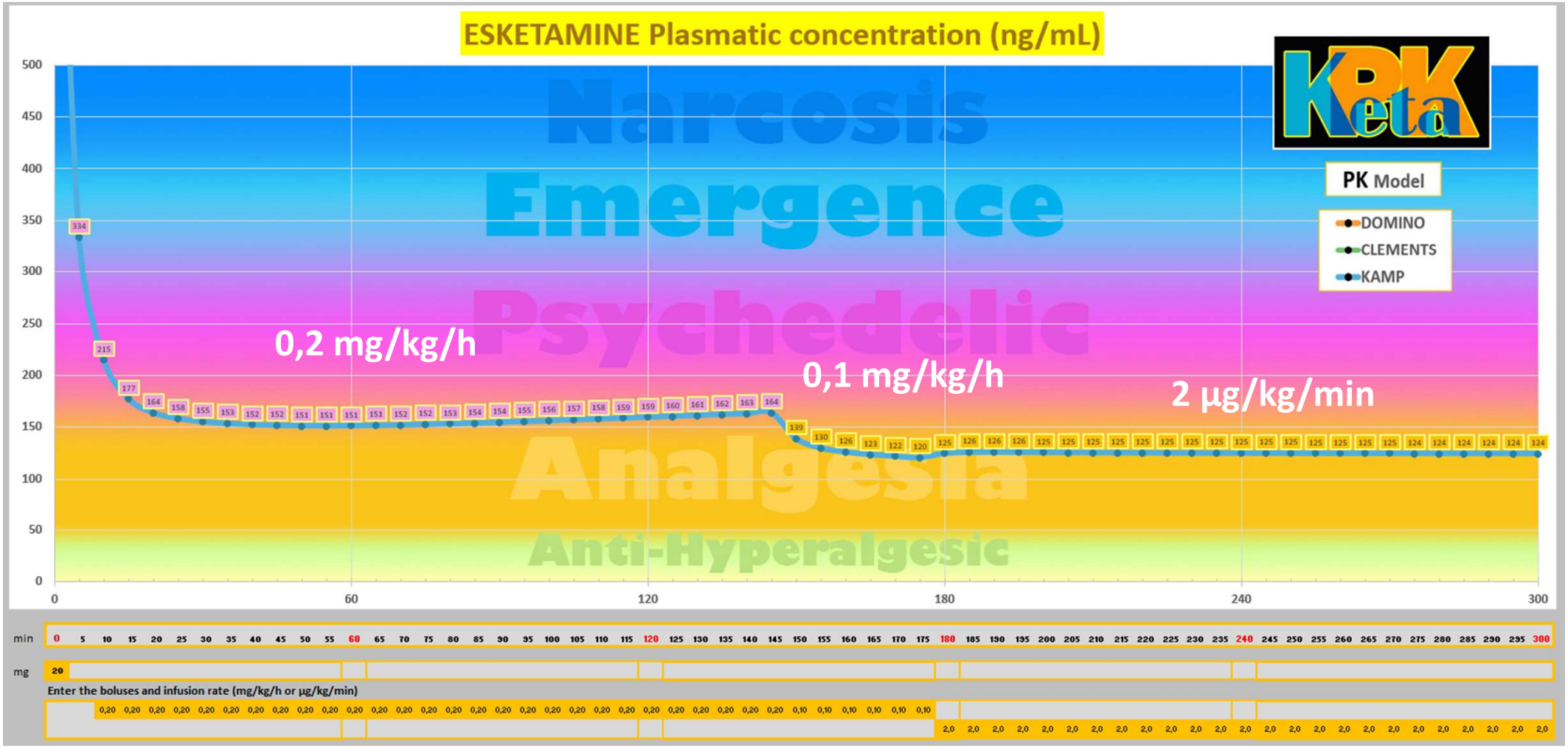
- **Relais au PSE** : **0,15 à 0,3 mg/Kg/h**

  On interrompt ou on diminue par deux la perfusion
  ~ 30 min avant la fin du geste chirurgical

- **Chez les patients les plus douloureux**
  les 2 premiers jours postopératoires
  - on peut continuer à administrer l'eskétamine au PSE
    0,06 à 0,15 mg/kg/h (4 à 10 mg/h)
  - ou, plus simplement, en PCA morphine **(0,5-1 mg/1 mg)**

Bolus 0,25 mg/kg

0,2 mg/kg/h (0,1 mg/kg/h 30 min avant la fin)



2 µg/kg/min = 0,12 mg/kg/min en post-op

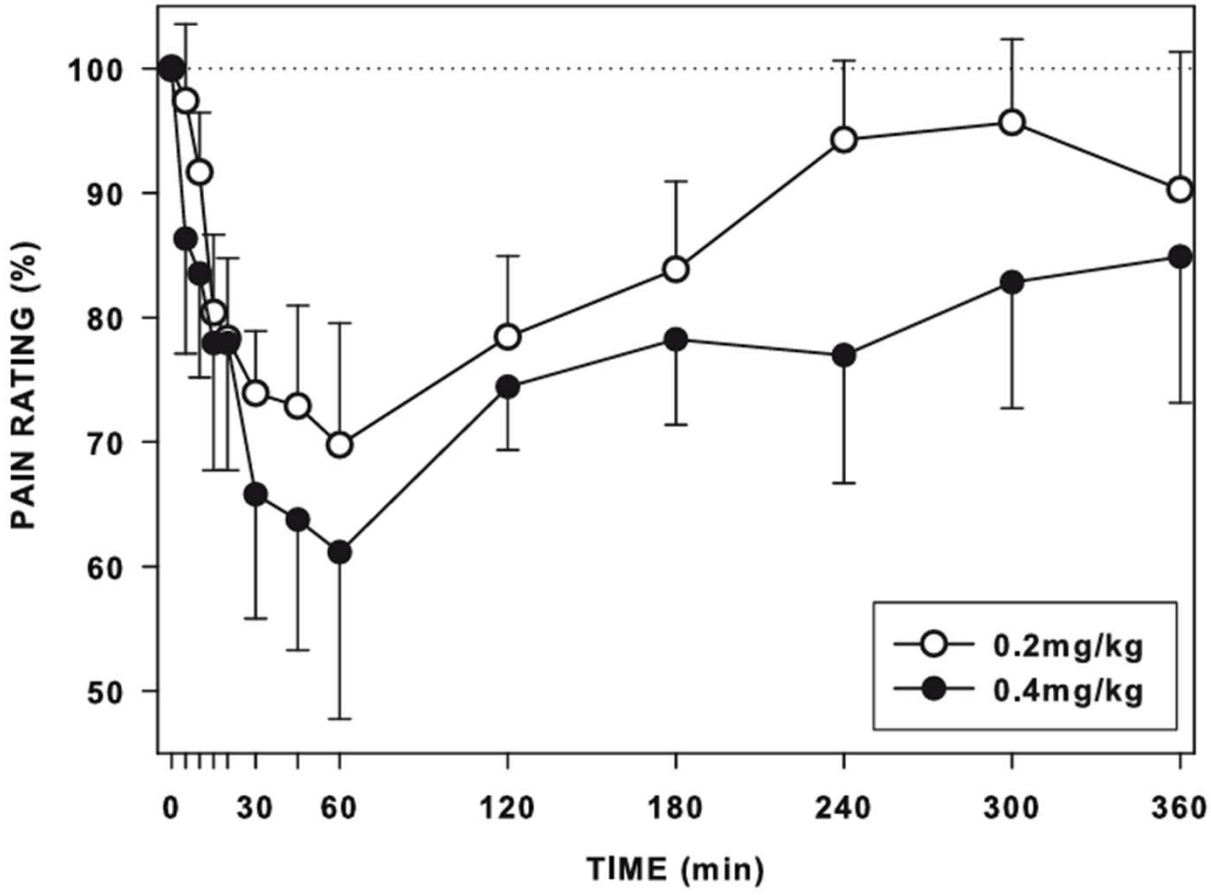
Et la douleur chronique ?

Effects of low-dose intranasal (S)-ketamine in patients with neuropathic pain

Volker Huge [a,*], Meike Lauchart [a], Walter Magerl [b], Gustav Schelling [a], Antje Beyer [a], Detlef Thieme [c], Shahnaz C. Azad [a]

European Journal of Pain 14 (2010) 387–394

Methods: Sixteen patients with neuropathic pain of various origins were randomized into two treatment groups: (S)-ketamine 0.2 mg/kg (group 1); (S)-ketamine 0.4 mg/kg (group 2). Plasma concentrations of (S)-ketamine and (S)-norketamine were measured over 6 h by High Performance Liquid Chromatography combined with mass spectrometry. Quantitative sensory testing (QST) was conducted before, during and after treatment. Side effects and amount of pain reduction were recorded.



En réanimation

Evaluation of Etomidate Use and Association with Mortality Compared with Ketamine Among Critically Ill Patients

2024

Hannah Wunsch , Nicholas A Bosch , Anica C. Law , Emily A. Vail , May Hua , Burton H Shen , Peter K. Lindenauer , David N Juurlink , Allan J. Walkey , and Hayley B Gershengorn

American Journal of Respiratory and Critical Care Medicine

Received: April 19, 2024 Accepted: August 21, 2024

Rationale: Uncertainty remains regarding the risks associated with single dose use of etomidate. Objectives: To assess use of etomidate in critically ill patients and compare outcomes for patients who received etomidate versus ketamine. Methods: We assessed patients who received invasive mechanical ventilation (IMV), admitted to an ICU in the Premier Healthcare Database, 2008-2021. The exposure was receipt of etomidate on the day of IMV initiation and the main outcome was hospital mortality. Using multivariable regression we compared patients who received IMV within the first two days of hospitalization who received etomidate with propensity-score matched patients who received ketamine. We also assessed whether receipt of corticosteroids in the days after intubation modified the association between etomidate and mortality. Measurements and Main Results: Of 1,689,945 patients who received IMV, nearly half (738,855; 43.7%) received etomidate. Among those who received IMV in the first two days of hospitalization, we established 22,273 matched pairs given either etomidate or ketamine. In the primary analysis, receipt of etomidate was associated with greater hospital mortality relative to ketamine (21.6% vs 18.7%; absolute risk difference: 2.8%, 95% CI 2.1%, 3.6%; adjusted odds ratio: 1.28, 95% CI 1.21,1.34). This was consistent across subgroups and sensitivity analyses. We found no attenuation of the association with mortality with receipt of corticosteroids in the days following etomidate use. Conclusions: Use of etomidate on the day of IMV initiation is common and associated with a higher odds of hospital mortality compared with ketamine. This finding is independent of subsequent treatment with corticosteroids.

Ketamine versus etomidate as an induction agent for tracheal intubation in critically ill adults: a Bayesian meta-analysis

2024

Takatoshi Koroki[1], Yuki Kotani[1,2,3*], Takahiko Yaguchi[1], Taisuke Shibata[1], Motoki Fujii[1], Stefano Fresilli[2], Mayuko Tonai[1], Toshiyuki Karumai[1], Todd C. Lee[4], Giovanni Landoni[2,3] and Yoshiro Hayashi[1]

Critical Care (2024) 28:48

Methods We searched MEDLINE, Embase, and the Cochrane Library from inception until April 27, 2023, for randomized controlled trials and matched observational studies comparing ketamine with any control in critically ill patients as an induction agent. The primary outcome was mortality at the longest follow-up available, and the secondary outcomes included Sequential Organ Failure Assessment score, ventilator-free days at day 28, vasopressor-free days at day 28, post-induction mean arterial pressure, and successful intubation on the first attempt. For the primary outcome, we used a Bayesian random-effects meta-analysis on the risk ratio (RR) scale with a weakly informative neutral prior corresponding to a mean estimate of no difference with 95% probability; the estimated effect size will fall between a relative risk of 0.25 and 4. The RR and 95% credible interval (CrI) were used to estimate the probability of mortality reduction (RR < 1). The secondary outcomes were assessed with a frequentist random-effects model. We registered this study in Open Science Framework (https://osf.io/2vf79/).

Results We included seven randomized trials and one propensity-matched study totaling 2978 patients. Etomidate was the comparator in all the identified studies. The probability that ketamine reduced mortality was 83.2% (376/1475 [25%] vs. 411/1503 [27%] RR, 0.93; 95% CrI, 0.79–1.08), which was confirmed by a subgroup analysis excluding studies with a high risk of bias. No significant difference was observed in any secondary outcomes.

Conclusions All of the included studies evaluated ketamine versus etomidate among critically ill adults requiring tracheal intubation. This meta-analysis showed a moderate probability that induction with ketamine is associated with a reduced risk of mortality.

ANESTHESIOLOGY 2024; 140:742–51

2024

ANESTHESIOLOGY

Etomidate *versus* Ketamine as Prehospital Induction Agent in Patients with Suspected Severe Traumatic Brain Injury

Floor J. Mansvelder, M.D., Sebastiaan M. Bossers, M.D., Stephan A. Loer, M.D., Ph.D., Frank W. Bloemers, M.D., Ph.D., Esther M. M. Van Lieshout, M.D., Ph.D., Dennis Den Hartog, M.D., Ph.D., Nico Hoogerwerf, M.D., Ph.D., Joukje van der Naalt, M.D., Ph.D., Anthony R. Absalom, M.B.Ch.B., M.D., Saskia M. Peerdeman, M.D., Ph.D., Carolien S. E. Bulte, M.D., Ph.D., Lothar A. Schwarte, M.D., Ph.D., Patrick Schober, M.D., Ph.D. for the BRAIN-PROTECT collaborators*

ANESTHESIOLOGY 2024; 140:742–51

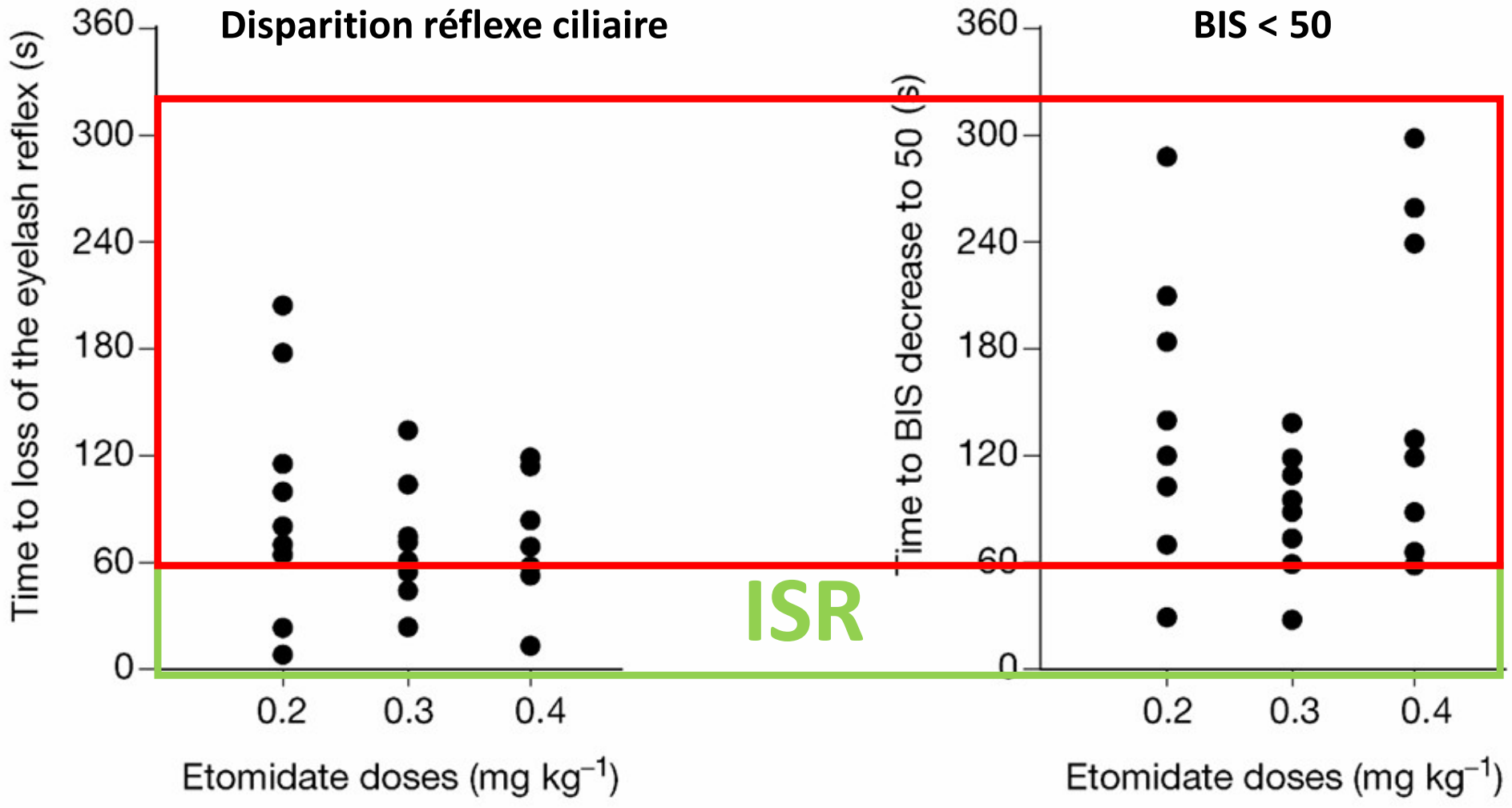
Methods: This study is a retrospective analysis of the prospectively collected observational data of the Brain Injury: Prehospital Registry of Outcomes, Treatments and Epidemiology of Cerebral Trauma (BRAIN-PROTECT) cohort study. Patients with suspected severe traumatic brain injury who were transported to a participating trauma center and who received etomidate or *S*(+)-ketamine for prehospital induction of anesthesia for advanced airway management were included. Statistical analyses were performed with multivariable logistic regression and inverse probability of treatment weighting analysis.

Results: In total, 1,457 patients were eligible for analysis. No significant association between the administered induction medication and 30-day mortality was observed in unadjusted analyses (32.9% mortality for etomidate *versus* 33.8% mortality for *S*(+)-ketamine; $P = 0.716$; odds ratio, 1.04; 95% CI, 0.83 to 1.32; $P = 0.711$), as well as after adjustment for potential confounders (odds ratio, 1.08; 95% CI, 0.67 to 1.73; $P = 0.765$; and risk difference 0.017; 95% CI, −0.051 to 0.084; $P = 0.686$). Likewise, in planned subgroup analyses for patients with confirmed traumatic brain injury and patients with isolated traumatic brain injury, no significant differences were found. Consistent results were found after multiple imputations of missing data.

Bispectral index changes following etomidate induction of general anaesthesia and orotracheal intubation

M.-A. Lallemand[1], C. Lentschener[1]*, J.-X. Mazoit[3], P. Bonnichon[2], I. Manceau[1] and Y. Ozier[1]

British Journal of Anaesthesia **91** (3): 341–6 (2003)



Racemic, S(+)- and R(−)-ketamine do not increase elevated intracranial pressure

A. Schmidt[1,2], I. Øye[3] and J. Åkeson[1,2]

*Acta Anaesthesiol Scand 2008; **52**: 1124–1130*

Lasting s-ketamine block of spreading depolarizations in subarachnoid hemorrhage: a retrospective cohort study

Santos *et al. Critical Care* (2019) 23:427

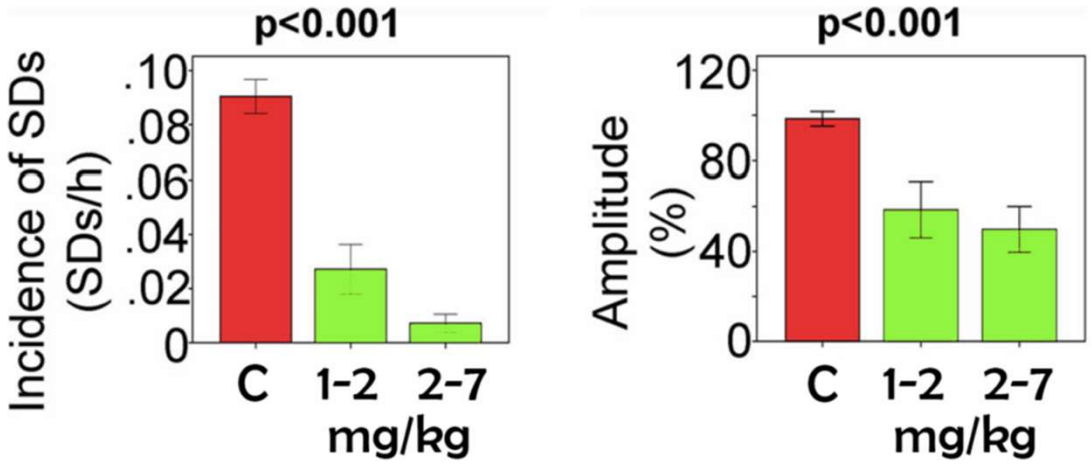
Methods: We performed a retrospective cohort study of 66 patients with aneurysmal subarachnoid hemorrhage (aSAH) from a prospectively collected database. Thirty-three of 66 patients received s-ketamine during

divided into low-dose (0.1–2.0 mg/kg BW/h) and high-dose (2.1–7.0 mg/kg/h)

Results: S-ketamine application started 4.2 ± 3.5 days after aSAH. The mean dose was 2.8 ± 1.4 mg/kg body weight (BW)/h and thus higher than the dose recommended for sedation. First, patients were divided according to

in patients receiving s-ketamine,

a significant decrease in SD incidence



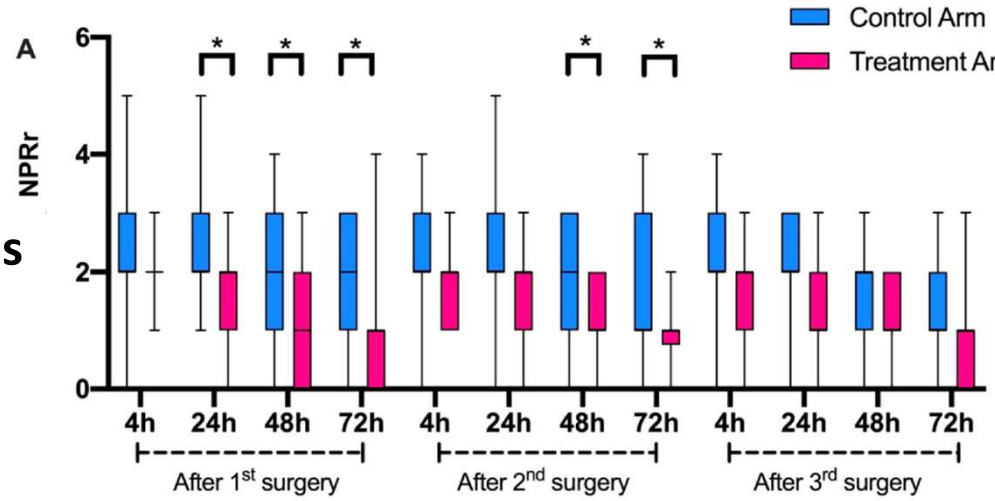
High-dose s-ketamine further significant decrease in SD incidence

Esketamine use for primary intelligent analgesia in adults with severe burns: A double-blind randomized trial with effects on analgesic efficacy, gastrointestinal function and mental state

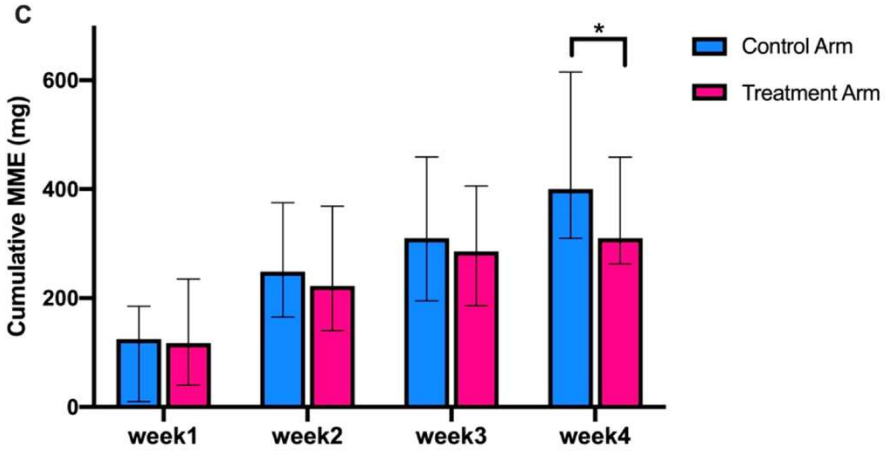
Qiulan He [a,1], *Qi Liu* [a,1], *Bing Liang* [b,1], *Xu Zhao* [a], *Wenqi Huang* [a], *Shaowei Gao* [a], *Caiyun Chen* [a], *Fei Zhou* [c], *Zhongxing Wang* [a,*]

N = 55

EVA repos



opioïdes



Eskétamine
Bolus 0,5 mg/Kg
+
Dans la PCA Suf
0,5 mg/kg/jour

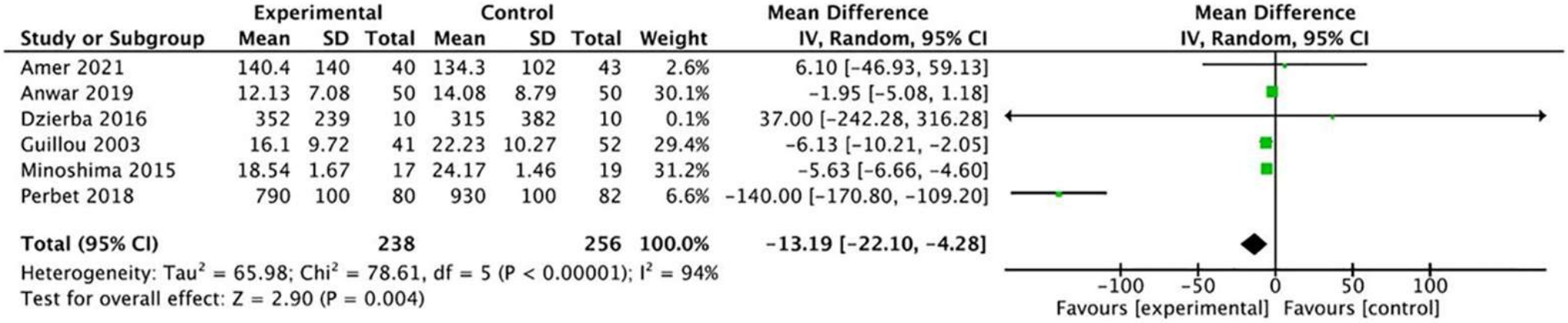
pour chaque acte chirurgical
(au total 9 jours)

Impact of Ketamine on Analgosedative Consumption in Critically Ill Patients: A Systematic Review and Meta-Analysis

Annals of Pharmacotherapy
2022, Vol. 56(10) 1139–1158

Katalina Chan, PharmD[1,2], Lisa D. Burry, PharmD[3,4], Christopher Tse, PharmD[5], Hannah Wunsch, MD, MSc[6,7], Charmaine De Castro, MI[8], and David R. Williamson, BPharm, PhD[9,10]

synthesis: A total of 13 RCTs, 5 retrospective, and 1 prospective cohort study were included (2255 participants). The primary analysis of six RCTs demonstrated reduced opioid consumption with ketamine regimens (n = 494 participants, −13.19 μg kg^{-1} h^{-1} morphine equivalents, 95% CI −22.10 to −4.28, P = 0.004). No significant difference was observed in sedative consumption, duration of mechanical ventilation (MV), ICU or hospital length of stay (LOS), intracranial pressure, and mortality. Small sample size of studies may have limited ability to detect true differences between groups.



Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Amer 2021	140.4	140	40	134.3	102	43	2.6%	6.10 [-46.93, 59.13]
Anwar 2019	12.13	7.08	50	14.08	8.79	50	30.1%	-1.95 [-5.08, 1.18]
Dzierba 2016	352	239	10	315	382	10	0.1%	37.00 [-242.28, 316.28]
Guillou 2003	16.1	9.72	41	22.23	10.27	52	29.4%	-6.13 [-10.21, -2.05]
Minoshima 2015	18.54	1.67	17	24.17	1.46	19	31.2%	-5.63 [-6.66, -4.60]
Perbet 2018	790	100	80	930	100	82	6.6%	-140.00 [-170.80, -109.20]
Total (95% CI)			**238**			**256**	**100.0%**	**-13.19 [-22.10, -4.28]**

Heterogeneity: Tau² = 65.98; Chi² = 78.61, df = 5 (P < 0.00001); I² = 94%
Test for overall effect: Z = 2.90 (P = 0.004)

Mean morphine equivalent dose (ME) (μg kg^{-1} h^{-1}).

Acute and Critical Care

Acute and Critical Care 2024 February 39(1):34-46
https://doi.org/10.4266/acc.2023.00829

The impact of ketamine on outcomes in critically ill patients: a systematic review with meta-analysis and trial sequential analysis of randomized controlled trials

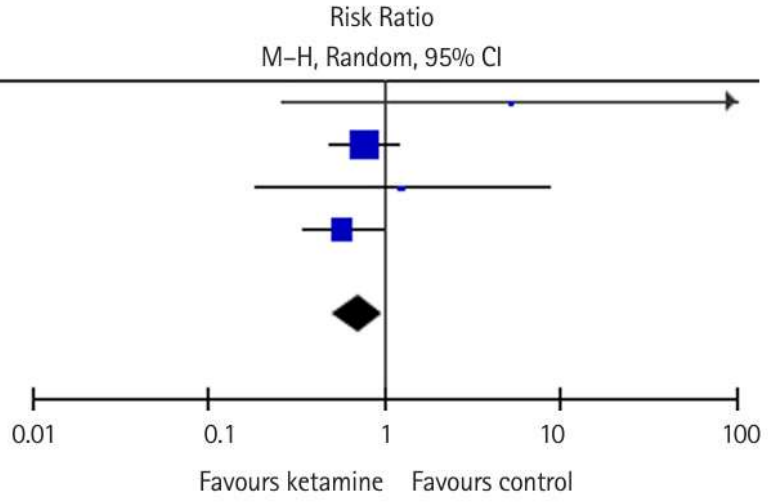
Yerkin Abdildin[1], Karina Tapinova[2], Assel Nemerenova[1], Dmitriy Viderman[3,4]

Results: Twelve RCTs involving 805 ICU patients (ketamine group, 398; control group, 407) were included in the meta-analysis. The ketamine group was not superior to the control group in terms of mortality, pain, mean and cumulative opioid consumption, midazolam consumption, and ICU length of stay. However, the model favored the ketamine group over the control group in delirium

Study or Subgroup	Ketamine Events	Ketamine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Amer et al., 2021	2	40	0	43	1.2%	5.37 [0.27, 108.47]
Dzierba et al., 2016	7	10	9	10	53.2%	0.78 [0.49, 1.23]
Guillou et al., 2003	2	41	2	52	3.0%	1.27 [0.19, 8.62]
Perbet et al., 2018	17	80	30	82	42.6%	0.58 [0.35, 0.97]
Total (95% CI)		**171**		**187**	**100.0%**	**0.71 [0.51, 0.99]**
Total events	28		41			

Heterogeneity: $Tau^2=0.00$; $Chi^2=2.84$, df=3 (P=0.42); $I^2=0\%$

Test for overall effect: Z=1.99 (P=0.05)



INFORMATION TRANSMISE SOUS L'AUTORITE DE L'ANSM

Hépatotoxicité

Juillet 2017

Kétamine : risque d'atteintes hépatiques graves lors d'utilisations prolongées et/ou à doses élevées

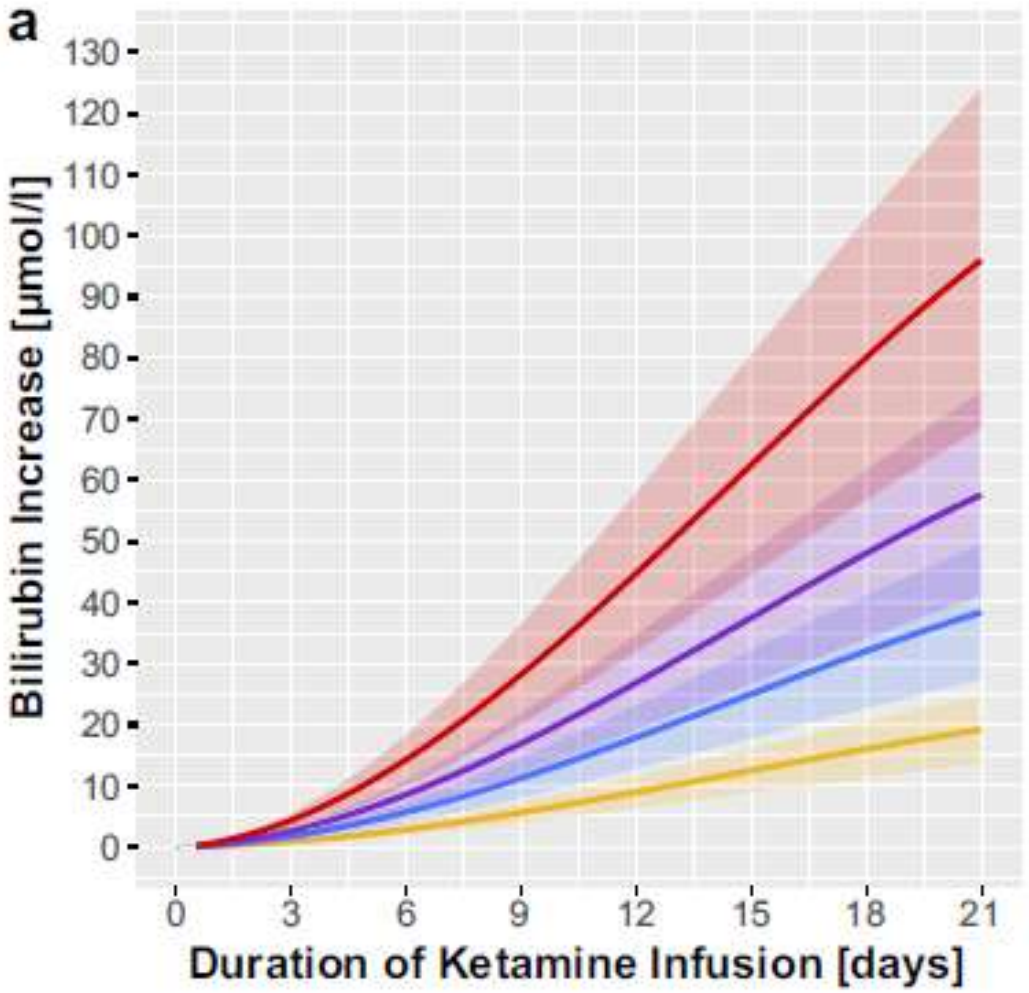
Information destinée aux anesthésistes réanimateurs, aux centres de prise en charge de la douleur, aux centres de prise en charge de brûlés, aux pharmaciens hospitaliers

- **Dix cas d'atteintes hépatiques graves, survenus depuis 2014, dont quatre ayant conduit à une transplantation hépatique, ont été rapportés récemment à l'ANSM.**
- **Ces atteintes cholestatiques de type cholangite sont susceptibles d'être liées à l'administration de kétamine de façon répétée et/ou prolongée (entre 1 et 5 mois de traitement continu) et à des posologies élevées, dans la prise en charge de douleurs rebelles (dépassant 100 mg/j en continu sur plusieurs jours) et lors de la réalisation de soins douloureux (200 à 400 mg/h en 3 à 6 heures) chez des grands brûlés.**

Long-term ketamine infusion-induced cholestatic liver injury in COVID-19-associated acute respiratory distress syndrome

Critical Care (2022) 26:148

Pedro David Wendel-Garcia[1†], Rolf Erlebach[1†], Daniel Andrea Hofmaenner[1], Giovanni Camen[1], Reto Andreas Schuepbach[1], Christoph Jüngst[2], Beat Müllhaupt[2], Jan Bartussek[1,3], Philipp Karl Buehler[1], Rea Andermatt[1†] and Sascha David[1*†]



Racémique

Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU

Critical Care Medicine September 2018 • Volume 46 • Number 9

John W. Devlin, PharmD, FCCM (Chair)[1,2]; Yoanna Skrobik, MD, FRCP(c), MSc, FCCM (Vice-Chair)[3,4]; Céline Gélinas, RN, PhD[5]; Dale M. Needham, MD, PhD[6]; Arjen J. C. Slooter, MD, PhD[7]; Pratik P. [10]; Mark E. Michele sma, MD[20,21]; Nathanie [26]; Xavier D Aaron M e, DO[33]; Sharon M Jean-Fra CM[38]; Richard Yahya Sh Chris Winkelman, RN, PhD, FCCM[45]; John L. Centofanti, MD, MSc[46]; Carrie Price, MLS[47]; Sina Nikayin, MD[45]; Cheryl J. Misak, PhD[46]; Pamela D. Flood, MD[47]; Ken Kiedrowski, MA[48]; Waleed Alhazzani, MD, MSc (Methodology Chair)[16,49]

Ketamine.

Question: Should ketamine be used as an adjunct to an opioid (vs an opioid alone) for pain management in critically ill adults?

Recommendation: We suggest using low-dose ketamine (0.5 mg/kg IVP x 1 followed by 1-2 μg/kg/min infusion) as an adjunct to opioid therapy when seeking to reduce opioid consumption in postsurgical adults admitted to the ICU (conditional recommendation, very low quality of evidence).

ESKESIA 5 mg/mL, solution injectable/pour perfusion

• Pour l'analgésie dans la respiration artificielle (patients en soins intensifs intubés), 0,25 mg d'eskétamine/kg sont généralement utilisées en bolus suivi d'une perfusion continue de 0,2 à 0,5 (jusqu'à 1,5) mg d'eskétamine/kg/h avec une administration simultanée de benzodiazépine.

• Lorsqu'il est utilisé en perfusion continue pour l'analgésie dans la respiration artificielle, la durée du traitement ne doit pas dépasser 4 à 6 semaines.

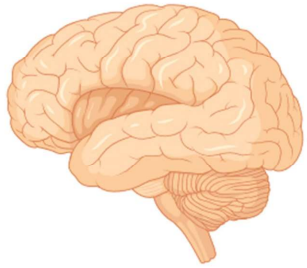
KETAMINE RENAUDIN 10 mg/mL, solution injectable

Analgésie pour des soins douloureux en soins intensifs ou en situation palliative

En association au midazolam, 15 à 20 minutes avant les soins : kétamine 0,5 à 1 mg/kg, en titration 25 mg par 25 mg en IV lente de 2 minutes et midazolam 0,01 à 0,05 mg/kg en IV lente de 2 minutes.

Conclusion (pharmacologie)

ANALGESIE ANESTHESIE

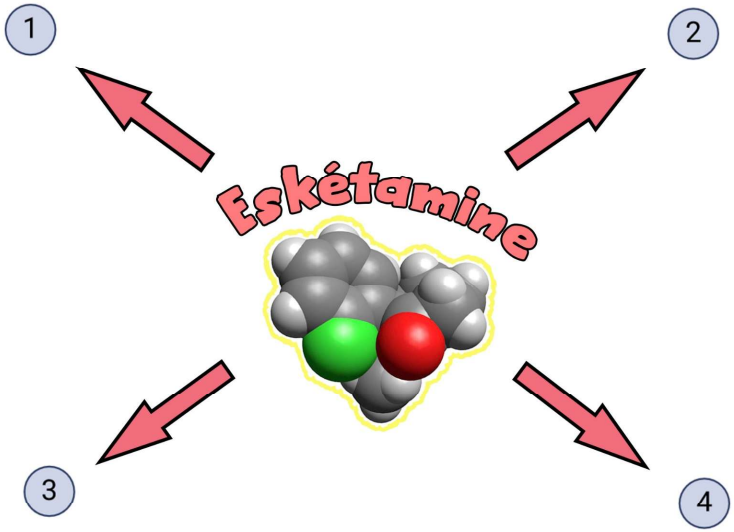


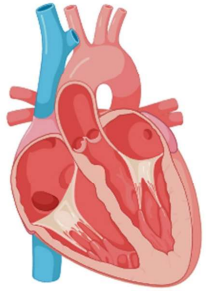
Puissance hypnotique,
et analgésique x 2

EFFETS PSYCHOACTIFS

Incidence comparable
Mais moins de déficits cognitifs

Réveil plus rapide

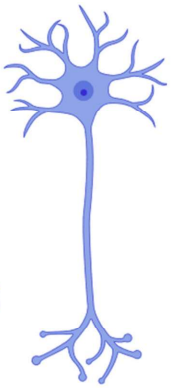




Préserve
* le préconditionnement ischémique
* la vasodilatation induite par l'hypoxie

CIRCULATION

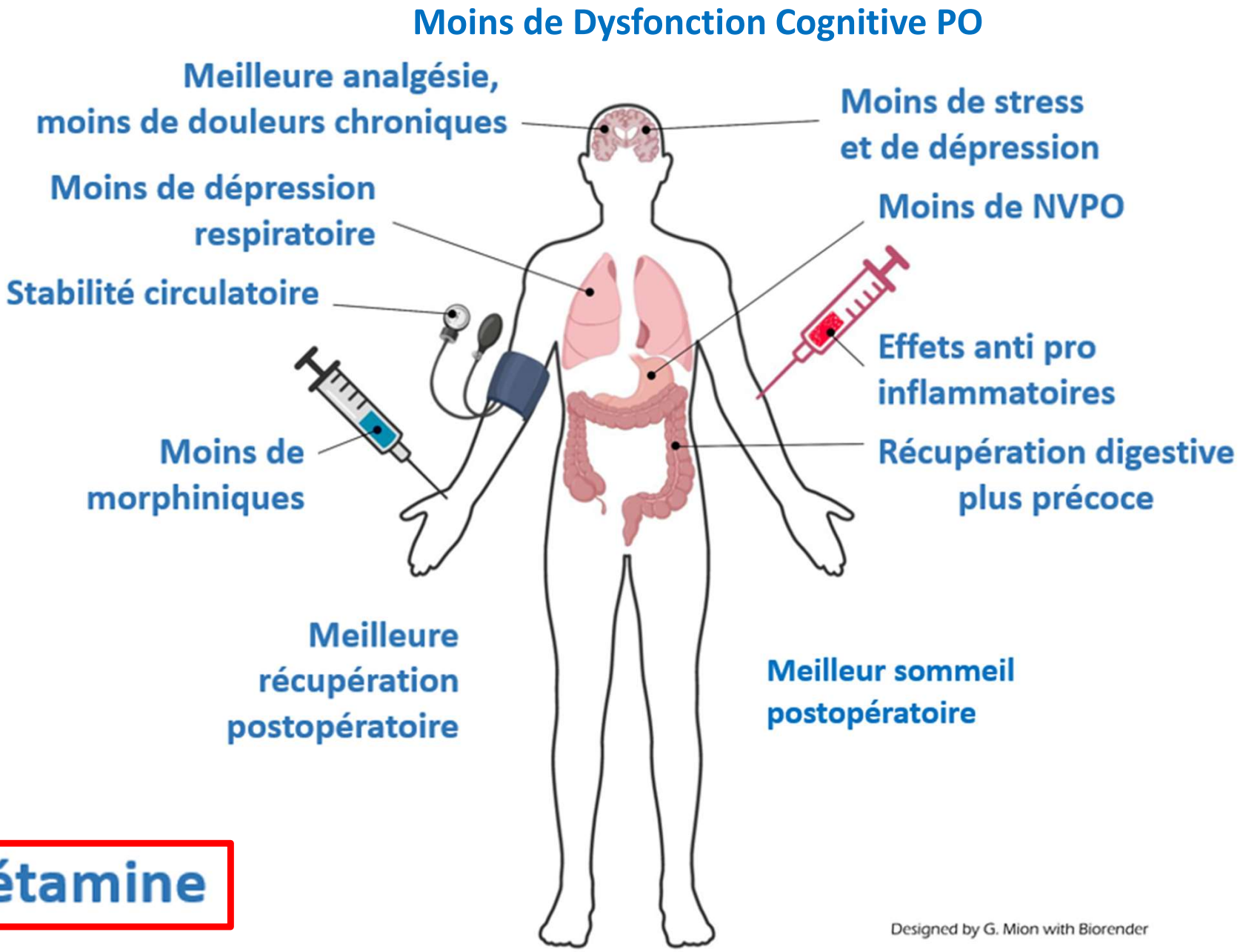
Experimentalemet
Neuroprotection
Neurorégénération



NEUROPROTECTION

Designed by G. Mion with avogadro and biorender

Conclusion (clinique)



eskétamine

GEORGESMION.COM

ESKÉTAMINE

Mion G, Bouatrous Wafa, Samama CM.
Esketamine – propofol anesthesia for elective cardioversion in atrial fibrillation
(Association eskétamine – propofol pour la cardioversion de la fibrillation atriale).
Canadian Journal of Anesthesia 2026; accepted for publication

Mion G.
Esketamine: Essential Differences Compared to Worldwide Used Racemic Ketamine and a Synopsis of its Peri-operative Benefits and Safety
Chap. 26 In: Himmelseher S. Neurobiology and New Clinical Uses for Ketamine.
Springer Nature Neuro-Methods. Editor: W. Walz, Saskatoon, Canada. 2025. P 499-530.

Mion G, Himmelseher S.
Esketamine: less drowsiness, more analgesia. Narrative review.
Anesthesia & Analgesia 2024;139:78–91

Mion G.
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Congrès de la SFMU, session « Analgésie : quelles évolutions à prévoir ? »
5-7 juin 2024, Paris, Palais des congrès de la porte Maillot.

Mion G.
La kétamine et l'eskétamine pour la prise en charge de la douleur chronique
Mémoire pour le laboratoire IDD, 2024.

Mion G.
Eskétamine, clé du récepteur NMDA.
Conférence au symposium CDM LAVOISIER / IDD, 23e congrès de la SFETD, Saint-Malo, 24 novembre 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**

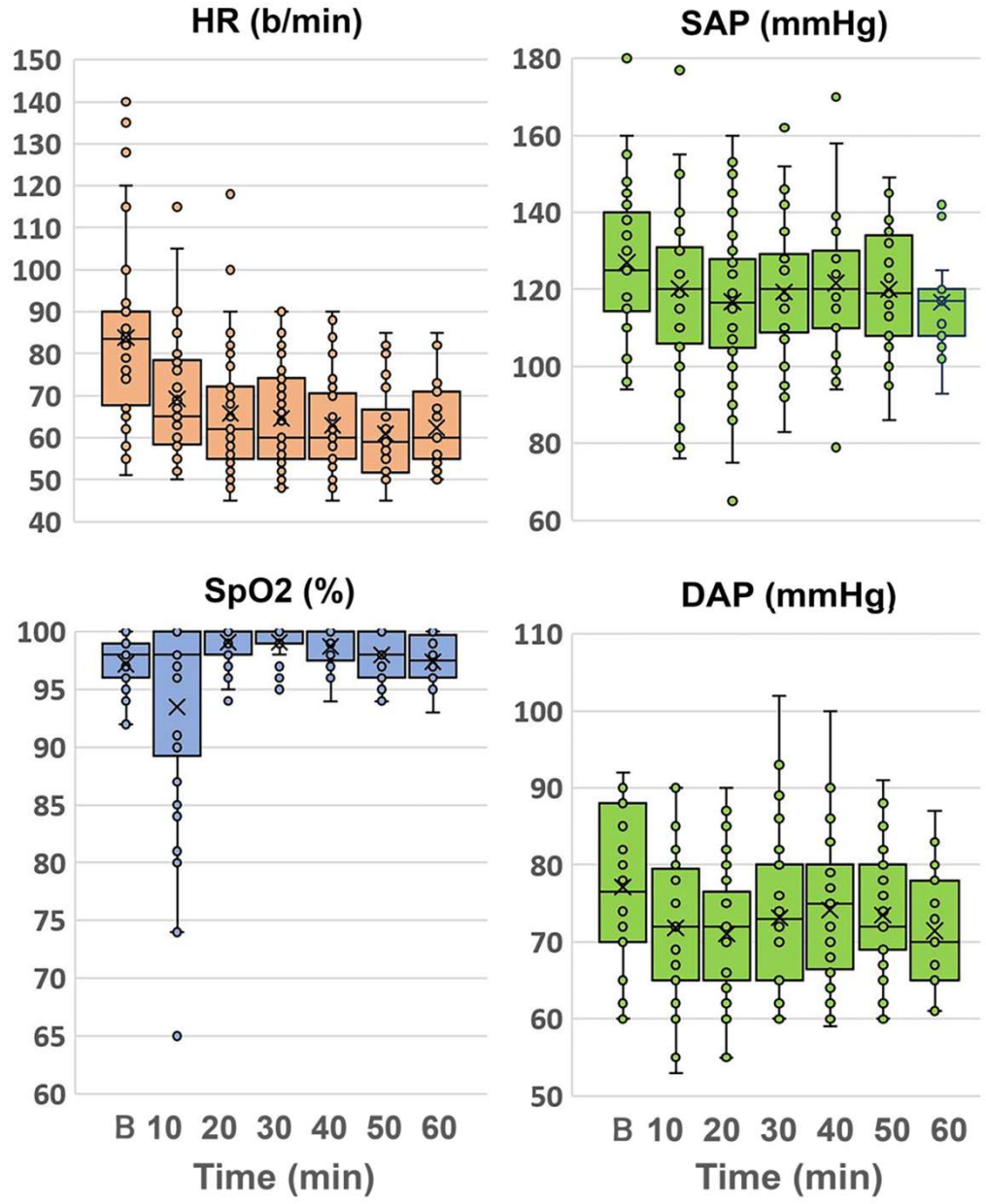
Proposition de **protocoles pour la douleur chronique** (hors AMM)

BIBLIOGRAPHIE

A propos de la fameuse (fumeuse ?) **note eskétamine de la SFAR**

Canadian Journal of Anesthesia/Journal canadien d'anesthésie

Esketamine - propofol anesthesia for elective cardioversion in atrial fibrillation



N = 43 (73 ans, FE<40% = 31%)

Eskétamine = 0,29 ± 0,04 mg/kg
Propofol = 1 mg/kg (0,86 - 1,28)
2 min avant le choc.

Succès = 95 % des cas
2 échecs (FEVG < 35 %)

Désaturation = 23% < 2 min (N = 9)
une seule apnée (10 min)
RR désat : > 75 ans = 47 % vs 4 %

Bradycardie = 0
4 hypotensions (9 %) < 10 min

Réveil = 13 ± 4 min, calme
47% ont rêvé,
jamais désagréables

19% vertiges brefs NVPO = 0