Alpha2 Agonistes en Anesthésie pédiatrique

Pr Souhayl DAHMANI. DAR Robert Debré. Paris.

Conflits d'intérêts

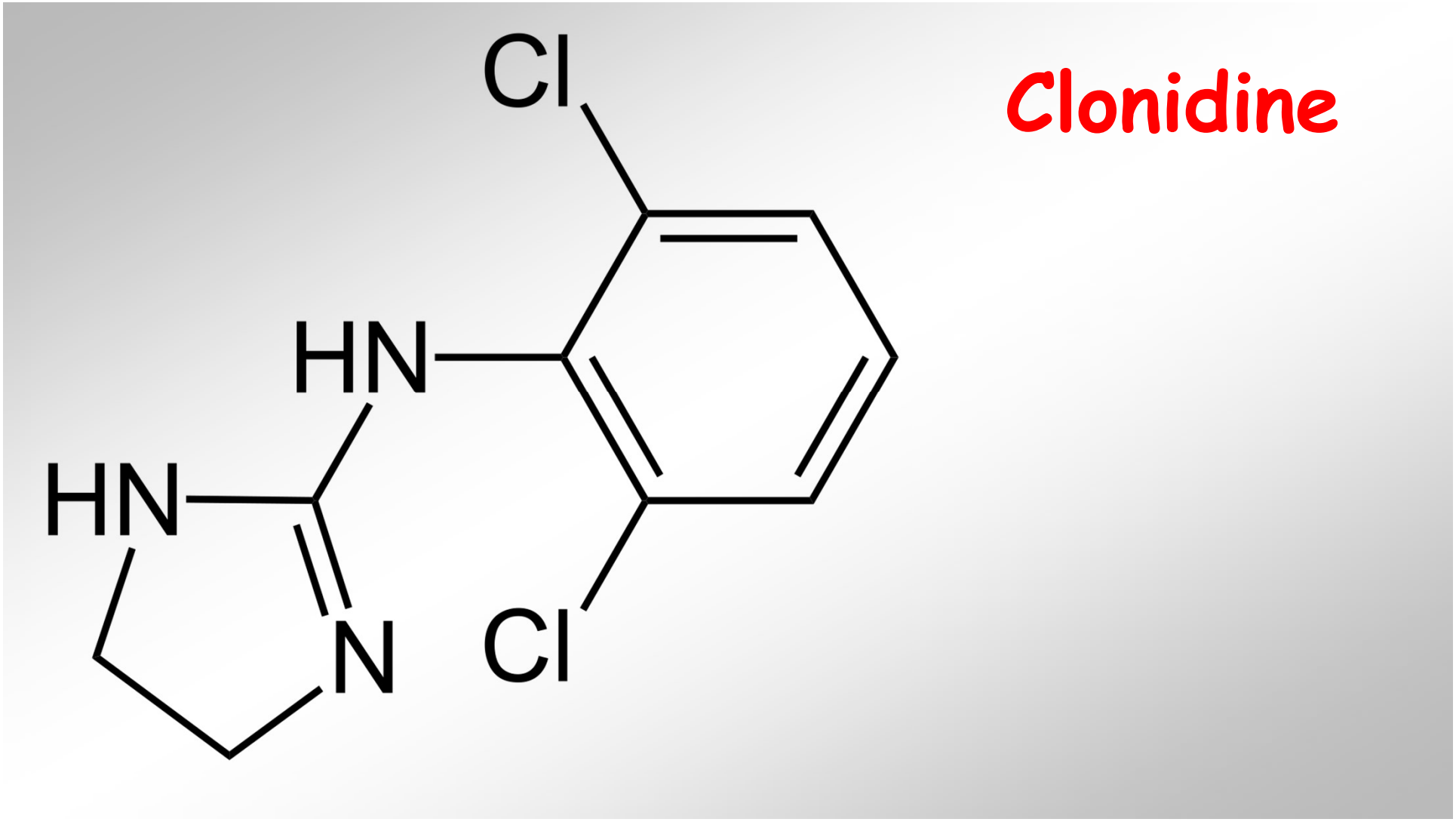
Aucun

Alpha2 Agonistes

Clonidine : a1/a2 sélectivité : 220/1,
Dexmedetomidine: a1/a2 sélectivité : 1620/1,

- Action sur 5 cibles
  - Alpha-1A : Vasoconstriction périphérique
  - Alpha-2A: Centraux, effet analgésique et sédatif
  - Alpha-2B: Localisation périphérique effet vasoconstricteur
  - Alpha-2C: Centraux régulation du largage de neurotransmetteurs
  - Récepteurs Imidazolés : effet hypotenseur

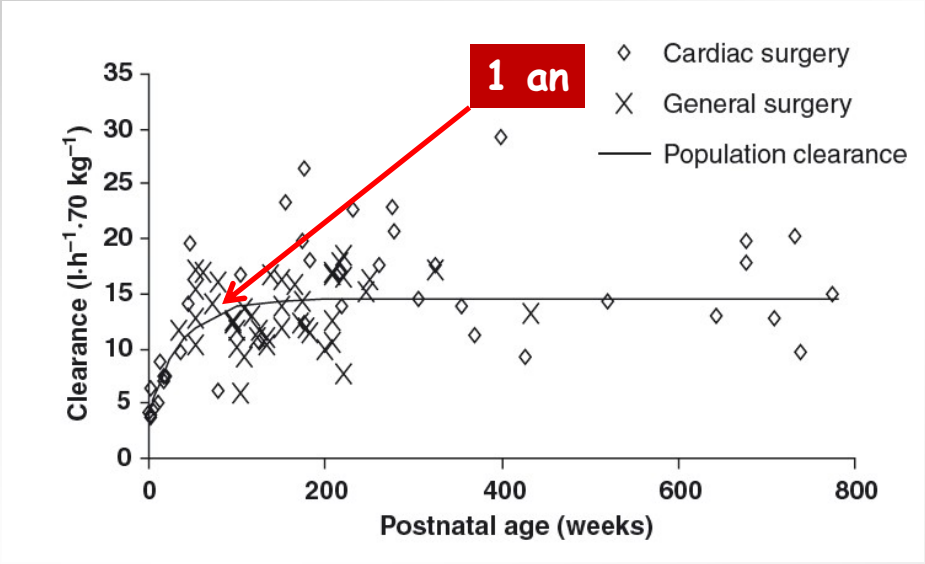
Afshari A et al. Curr Opin Anaesth 2019.
Giovannitti JA et al, Prog Anesth 2015.



Clonidine

Pharmacologie

Liaison protéique : 95 %
Biodisponibilité: Orale 85 % avec pic action 60 à 90 mn



Changes in context sensitive half-life with age following an infusion of 0.3 $\mu g \cdot kg^{-1}\ h^{-1}$

	1 h	*3 h*	*6 h*	*10 h*
Neonate	8	10.75	11.5	11.75
3 months	5.5	8	8.25	8.5
6 months	4.25	6.5	7	7.25
1 year	3.3	5.25	6	6.25
5 years	2.8	5.25	6	6.25
10 years	2.75	5.75	6.25	6.75
Adult	2.5	6.5	7.5	8.25

Potts AL et al. Pediatr Anesth 2007.
Afshari A . Curr Opin Annaesth 2019.

Pharmacologie

Concentration efficace pour analgésie & Sédation: 1,5 à 2 µg.l^{-1} adultes et enfant

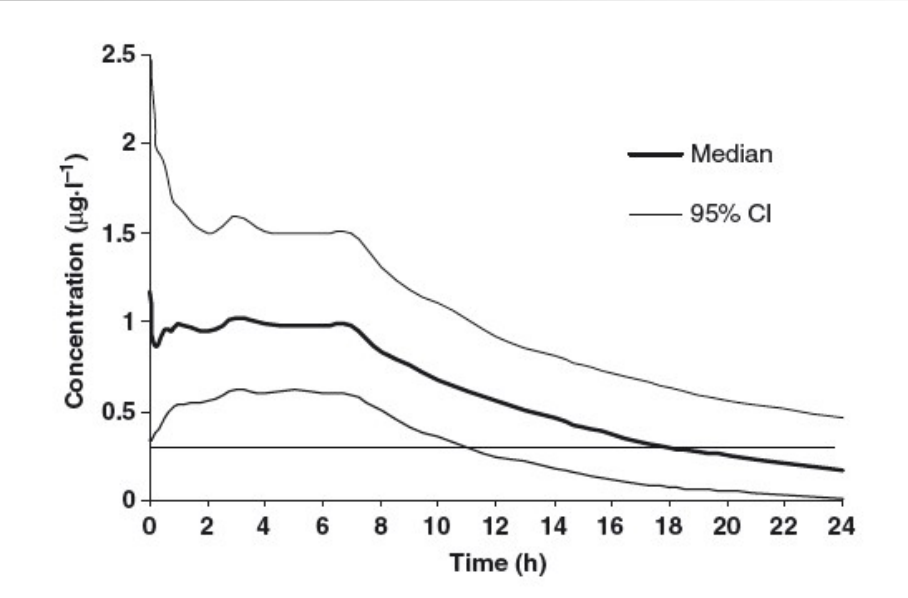


Schéma classique recommandé
1 µg.Kg^{-1}
Puis 2 µg.Kg^{-1}.h^{-1} pendant 30 mn
Puis 1 µg.Kg^{-1}.h^{-1} pendant 1 h
Puis 0,5 µg.Kg^{-1}.h^{-1} pendant 1 à 3 h

Potts AL et al. Pediatr Anesth 2009.

Utilisation

- Utilisation comme prémédication : prévention DPO
- Peu ou pas d'utilisation pendant la période intraopératoire
- Utilisation dans le domaine de l'anesthésie-locorégionale

Prémédication

Faibles doses : 0,5 µg.Kg^{-1}
Fortes doses à 2 à 4 µg.Kg^{-1} Orales ou 4 µg.Kg^{-1} en nasal

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo/no treatment	Clonidine				
Number requiring additional analgesia at any time postoperatively - low dose clonidine	867 per 1000	867 per 1000 (676 to 1000)	RR 1 (0.78 to 1.28)	45 (1 study)	⊕⊕⊖⊖ low[1,2]	
Number requiring additional analgesia at any time postoperatively - high dose clonidine	558 per 1000	134 per 1000 (61 to 285)	RR 0.24 (0.11 to 0.51)	205 (3 studies)	⊕⊕⊕⊖ moderate[3,4]	
Number requiring additional analgesia at any time postoperatively - high dose clonidine, studies with lower risk of bias	700 per 1000	168 per 1000 (63 to 483)	RR 0.24 (0.09 to 0.69)	160 (2 studies)	⊕⊕⊕⊖ moderate[1]	

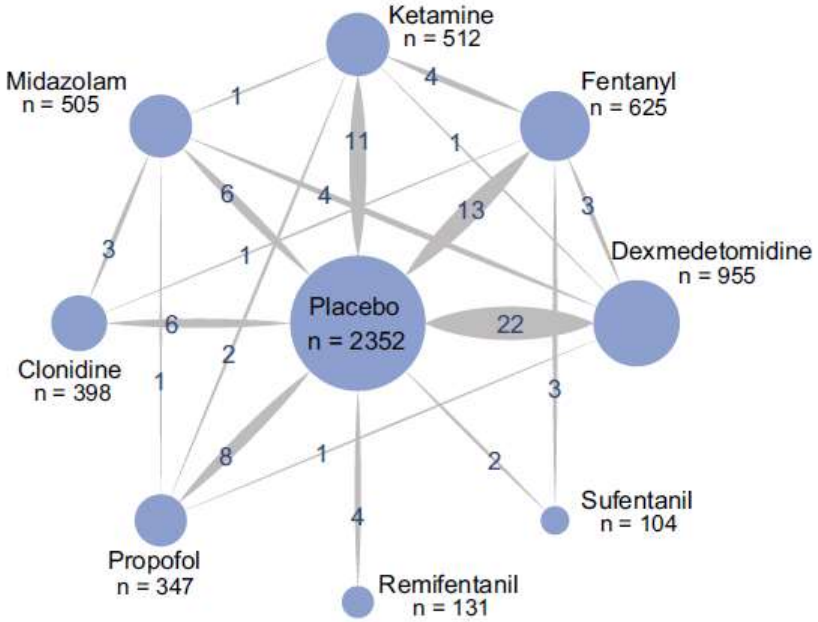
Lambert P et alet al. Cochrane database . CD 009633.

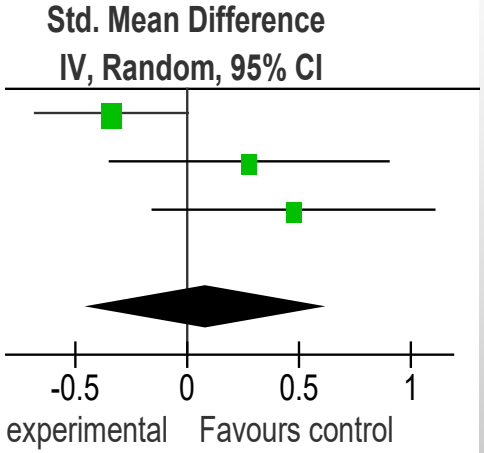
Prémédication

Study or Subgroup	Experim Mean	S
Fazi L, 2001	72	
Tazeroualti N, 2007_1	7	
Tazeroualti N, 2007_2	8	
Total (95% CI)		

Heterogeneity: Tau² = 0.16; Chi² = 6

Test for overall effect: Z = 0.30 (P =





Dahmani S al. Acta Ananesth Scand 2010.
Wang X et al, Mol Neurobiol 2016

Intraopératoire

Enfants 1 à 5 ans, *ASA* I & II
Clonidine 3 $\mu g.Kg^{-1}$ en IV 20 mn avant la fin de l'intervention

	Clonidine (n=187)		Placebo (n=183)		Risk ratio M-H, fixed (95% CI)
	Events	Total	Events	Total	
Boys	30	150	69	147	0·43 (0·30–0·61)
Girls	16	37	17	36	
Age <2 years	11	46	27	42	
Age ≥2 years	35	141	59	141	
Juliane Marie Centre	17	124	52	124	
Køge	3	13	3	11	
Vejle	26	50	31	48	

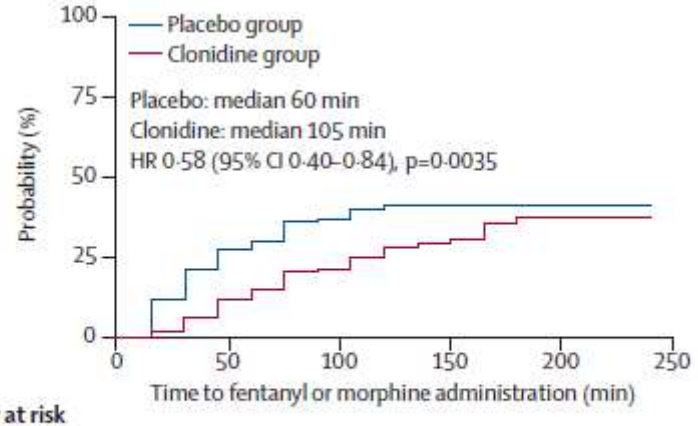
0·01 0·1 1 1

Favours clonidine Favours

Table 2: Duration of surgery, use of opioids, and pain score

es (clonidine vs placebo)

Girls	All



Number at risk (censored)

Placebo	180 (0)	113 (18)	53 (65)	14 (105)	1 (114)	0 (115)
Clonidine	189 (0)	158 (9)	108 (42)	58 (98)	12 (124)	2 (134)

Dahmani S al. Acta Ananesth Scand 2010.
Wang X et al, Mol Neurobiol 2016

ALR

Regional Anesthesia and Pain Medicine • Volume 43, Number 2, February 2018

The European Society of Regional Anaesthesia and Pain Therapy/American Society of Regional Anesthesia and Pain Medicine Recommendations on Local Anesthetics and Adjuvants Dosage in Pediatric Regional Anesthesia

Santhanam Suresh, MD, Claude Ecoffey, MD,† Adrian Bosenberg, MB, ChB, FFA(SA),‡ Per-Anne Lonnqvist, MD,§ Gildasio S. de Oliveira Jr, MD, MSCi,|| Oscar de Leon Casasola, MD,** José de Andrés, MD, PhD,†† and Giorgio Ivani, MD‡‡*

- Clonidine(1–2 μg/kg) and morphine (10–30 μg/kg) can be used intrathecally to prolong the duration of spinal blockade in children. Because toxicity data are very limited in children, the dose used should be the minimally necessary to achieve the benefits and minimize potential adverse effects. (Evidence A2)

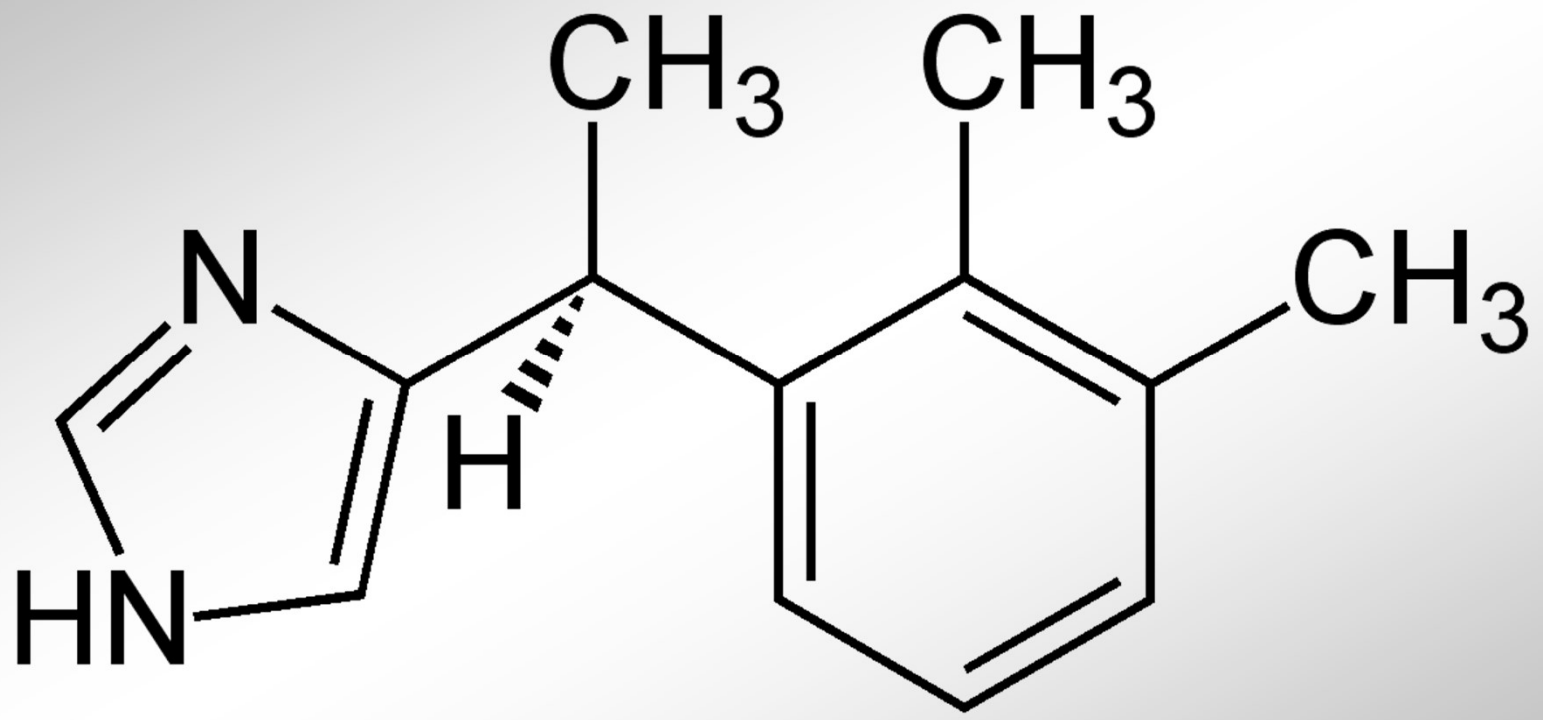
- Alpha-2 adrenoceptor agonists (eg, dexmedetomidine) can be used as an adjunct to prolong the duration of peripheral nerve blocks in children.[58] Because toxicity data are very limited in children, the dose used should be the minimally necessary to achieve the benefits and minimize potential adverse effects. (Evidence A1)

ALR

Clinical trial	Lundblad *et al.* 2015	Trifa *et al.* 2012	Trifa *et al.* 2010	Kaouech *et al.* 2008	Kaabachi *et al.* 2005
Peripheral block type	Ilioinguinal-iliohypogastric	Axillary brachial plexus	Saphenous and Sciatic	Penile	Ilioinguinal-iliohypogastric
No. of patients Adjunct/Plain	22/21	30/30	14/14	27/28	49/49
Age (years)	1.7–7.9	1–8	0.8–10	1–9	1–13
Weight (kg)	12–34	9–31	8–47	10–32	8–45
Gender M/F	30/13	33/27	17/11	54/0	98/0
Local anesthetic	Ropivacaine 0.2%	Ropivacaine 0.2%	Bupivacaine 0.25%	Bupivacaine 0.5%	Bupivacaine 0.25%
LA dose	0.2 ml·kg^{-1}	0.4 ml·kg^{-1}	0.2 and 0.3 ml·kg^{-1}	0.2 ml·kg^{-1}	0.3 ml·kg^{-1}
Adjunct	Dexmedetomidine	Clonidine	Clonidine	Clonidine	Clonidine
Adjunct dose	0.3 mcg·kg^{-1}	1 mcg·kg^{-1}	1 mcg·kg^{-1}	1 mcg·kg^{-1}	1 mcg·kg^{-1}
Pain scale (min-max)	CHIPPS/NRS (0–10)	CHEOPS (4–13)	CHEOPS (4–13)	CHEOPS (4–13)	Modified CHEOPS (0–10) VAS (0–100)
Trigger score for supplemental analgesia	≥4	>6	>7	≥7	4–5/30–50
Primary endpoint	Time to first administration of supplemental analgesia	Analgesia requirements during the first 24 h	Time to first administration of supplemental analgesia	Time to first administration of supplemental analgesia	Time to first administration of supplemental analgesia

Lumblad M al. Curr Opin Anaesth 2016.

Dexmedetomidine



Anesthesiology 2005; 103:969–77
© 2005 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

Effects of Dexmedetomidine on Hippocampal Focal Adhesion Kinase Tyrosine Phosphorylation in Physiologic and Ischemic Conditions

Souhayl Dahmani, M.D., Danielle Rouelle,† Pierre Gressens, M.D., Ph.D.,‡ Jean Mantz, M.D., Ph.D.§*



Anesthesiology 2008; 108:457–66
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Dexmedetomidine Increases Hippocampal Phosphorylated Extracellular Signal–regulated Protein Kinase 1 and 2 Content by an α_2-Adrenoceptor–independent Mechanism

Evidence for the Involvement of Imidazoline I1 Receptors

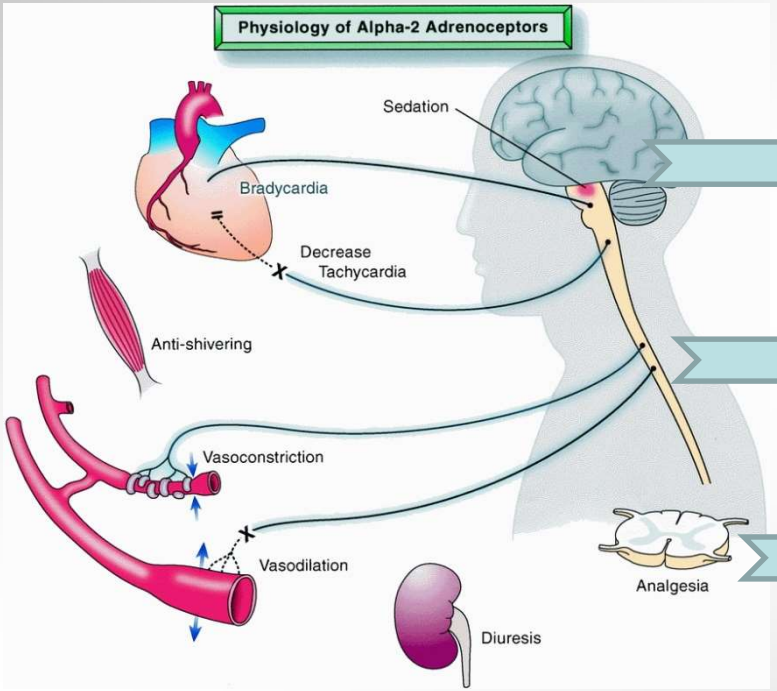
Souhayl Dahmani, M.D., Ph.D., Andrea Paris, M.D.,† Virginie Jannier, M.D.,* Lutz Hein, M.D.,‡ Danielle Rouelle,§ Jens Scholz, M.D., Ph.D.,‖ Pierre Gressens, M.D., Ph.D.,# Jean Mantz, M.D., Ph.D.***

Anesthesiology 2010; 112:373–83
Copyright © 2010, the American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins

Characterization of the Postconditioning Effect of Dexmedetomidine in Mouse Organotypic Hippocampal Slice Cultures Exposed to Oxygen and Glucose Deprivation

Souhayl Dahmani, M.D., Ph.D.,* Danielle Rouelle,† Pierre Gressens, M.D., Ph.D.,‡ Jean Mantz, M.D., Ph.D.§

Pharmacologie



Libération Noradrénaline → SEDATION, SYMPATHOLYSE

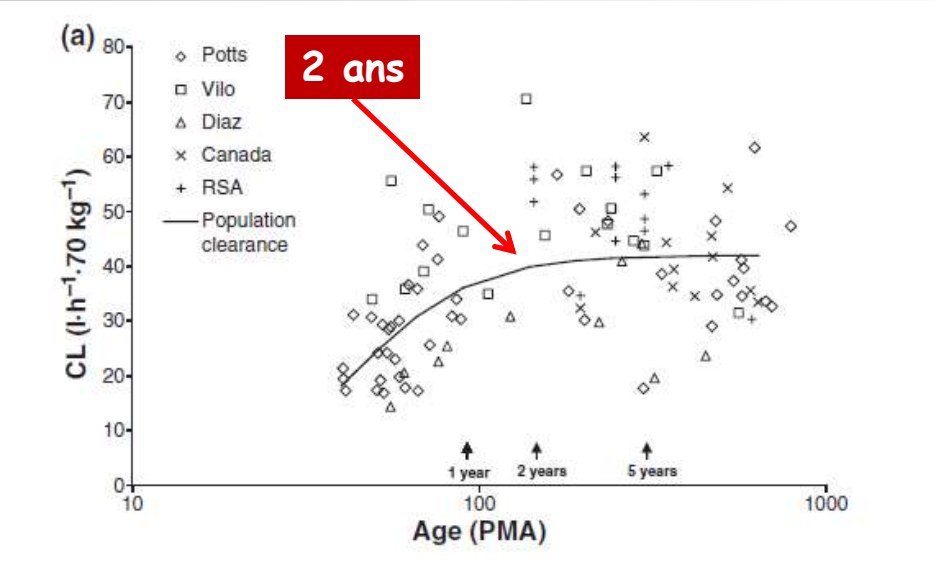
Récepteurs α2-Adrénergiques → ANALGESIE

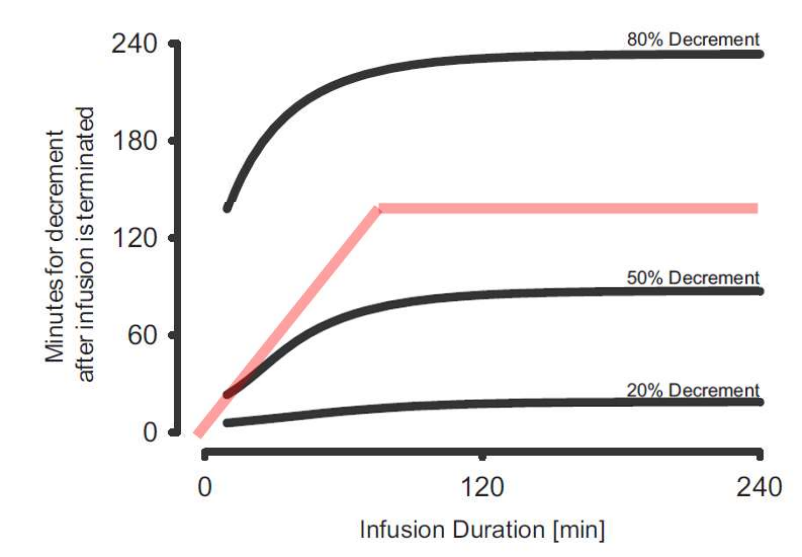
Hyperpolarisation & Libération substance P → ANALGESIE

Mantz J et al. Eur J Anaesth 2011.

Pharmacologie

Liaison protéique : 93 %
Biodisponibilité: Orale : 16 %; nasale: 65 %; Sublinguale: 85 %

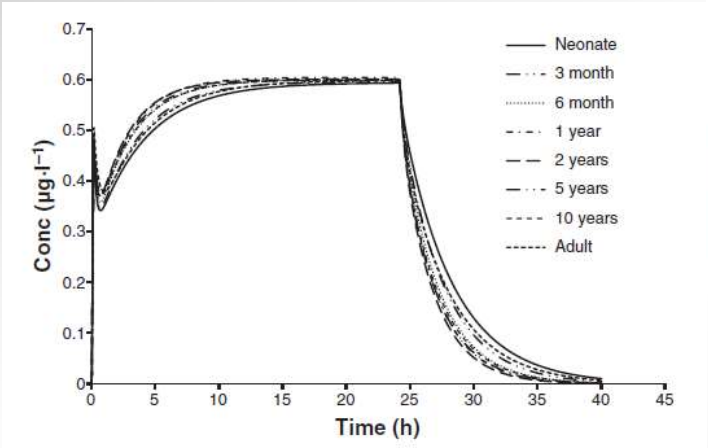




Potts AL et al. Pediatr Anesth 2009.
Mason KP. Anesth Analg 2011.
Petroz GC et al. Anesthesiology 2006.

Pharmacologie

Concentration efficace pour sédation: 0,6 µg.l^{-1} adultes
Concentration efficace pour sédation: 0,4 à 0,8 µg.l^{-1} pédiatrie



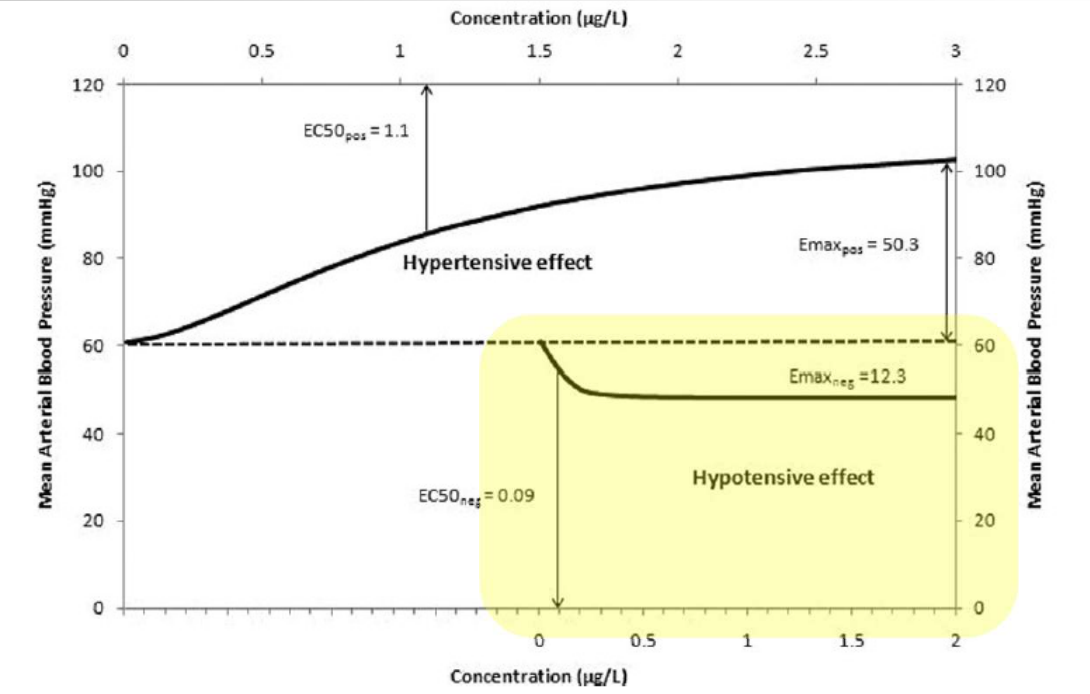
Age	Weight (kg)	Loading dose (µg·kg^{-1}·h^{-1})	Maintenance dose (µg·kg^{-1}·h^{-1}) general sedation	Maintenance dose (µg·kg^{-1}·h^{-1}) postoperative cardiac infusion
Neonate	3.5	2.9	0.33	0.24
3 month	6	2.9	0.40	0.29
6 month	7.5	2.9	0.46	0.34
1 year	10	2.9	0.51	0.37
2 year	12	2.9	0.53	0.39
5 year	20	2.9	0.49	0.36
8 years	25	2.9	0.47	0.34
20 years	70	2.9	0.36	0.26

Schéma classique recommandé
1 µg.Kg^{-1} en 10 à 20 mn puis 0,4 µg.Kg^{-1}.h^{-1}

Potts AL et al. Pediatr Anesth 2009.
Mason KP. Anesth Analg 2011.

Hémodynamique

Faible concentration: effet sympatholytique
Forte concentration: effet sympathomimétique



Potts AL et al. Pediatr Anesth 2010.

Hémodynamique

Bradycadrie = baisse de 20 % par rapport baseline

Parameter	Studies	Patients	Effect size (95% CI)	I^2 (%)	I^2 after sensitivity analyses (%)
Mean change in heart rate	13	1702	−17.26 (−21.60, −12.92); $P < 0.00001$	95	71
Subgroup analyses					
Age groups					
1–5 years	5	636	−19.98 (−24.37, −15.58); $P < 0.00001$	94	51
6–10 years	5	223	−14.75 (−28.33, −1.16); $P < 0.05$	97	74
11–18 years	2	32	−10.88 (−20.76, −1.00); $P < 0.05$	95	–

Gong M et al. Int J Clin Pharmacol 2019.

Warning !!

AMM : Dexor®

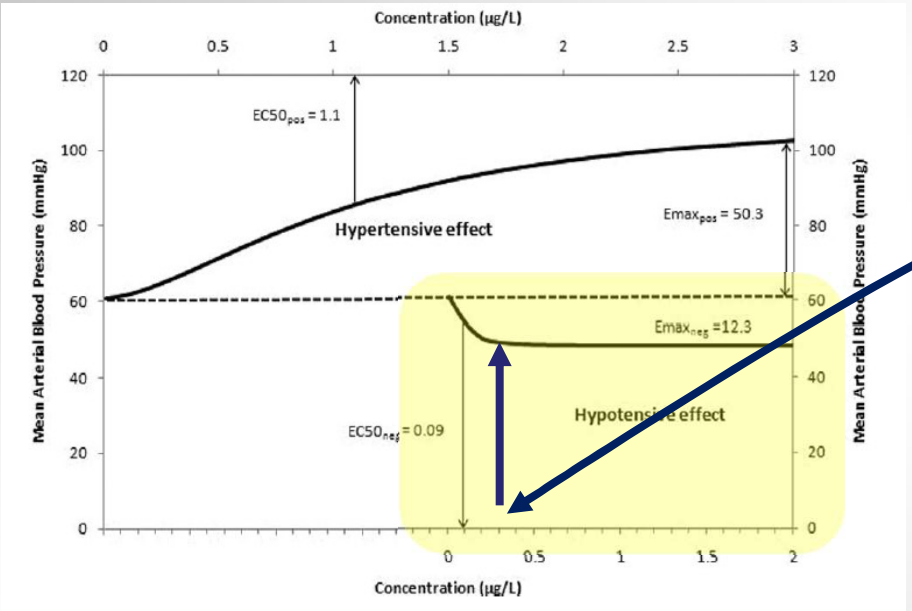
- **Sédation adultes en USI :**
  - Sédation pas plus profond que celui permettant une réponse à un stimulus verbal.
  - Dose initiale de 0,7 µg/kg/h qui pourra être ajustée par paliers allant de 0,2 à 1,4 µg/kg/h
  - La dose maximale de 1,4 µg/kg/h
  - Durée limitée à 14 jours. L'utilisation de Dexdor® sur une période plus longue devra être réévaluée régulièrement.
- **Sédation adultes non intubés avant et/ou pendant les actes à visée diagnostique ou chirurgicale :**
  - Sédation pas plus profond que celui permettant une réponse à un stimulus verbal.
  - Dose initiale de 0,5 à 1 µg/kg en 10 minutes
  - Entretien à 0,6 à 0,7 µg/kg/h ajustement de 0,1 à 0,2 µg/kg/h

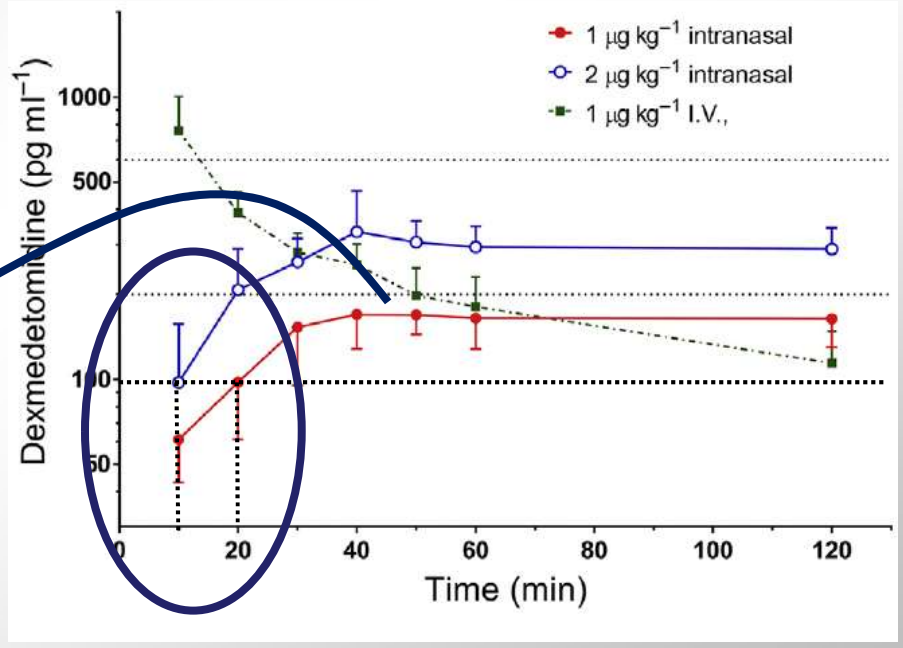
Utilisation

- Utilisation comme prémédication
- Utilisation en combinaison avec d'autres agents sédatifs/anesthésiques et analgésiques au bloc opératoire:
- Utilisation comme agent sédatif pour l'anesthésie procédurale
- Utilisation dans le domaine de l'anesthésie-locorégionale

Prémédication

Dose 1 $\mu g.Kg^{-1}$ intra-nasal (dose efficace sédation : 100 $pg.ml^{-1}$)

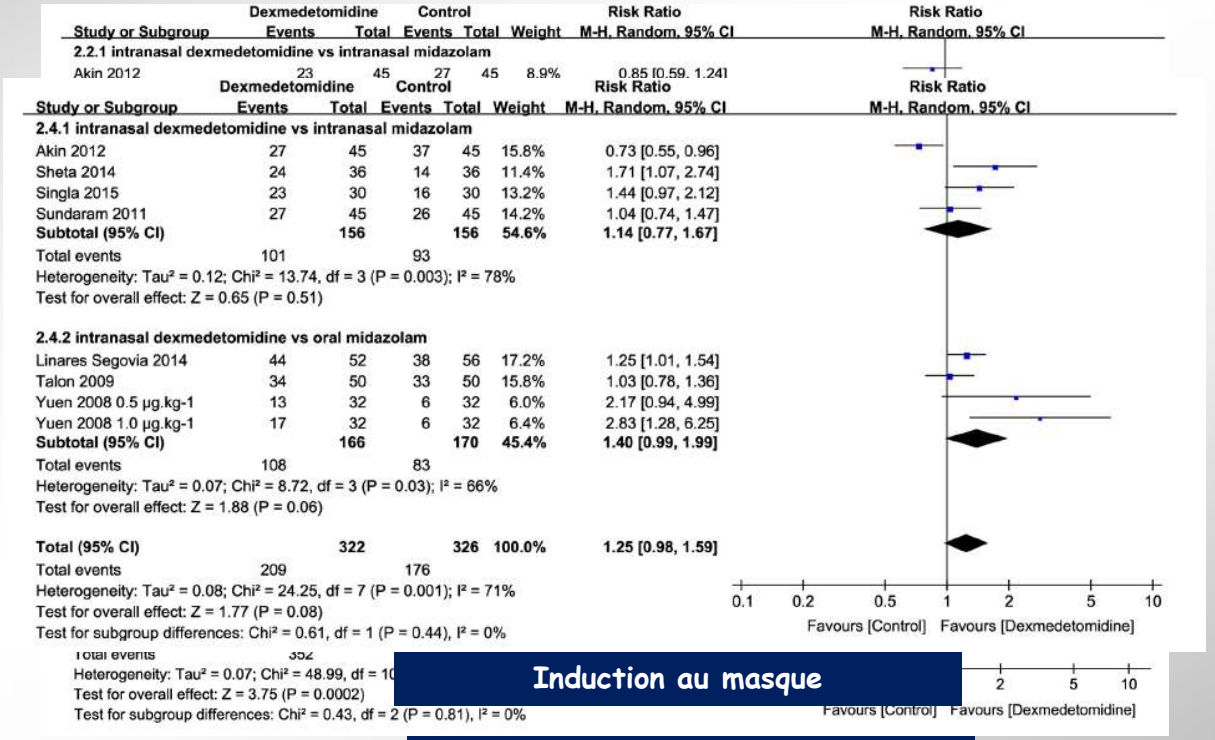




Miller JW et al. Br J Anaesth 2018.

Prémédication

Intranasale: Dose 1 $\mu g.Kg^{-1}$ 30 à 60 minutes avant bloc



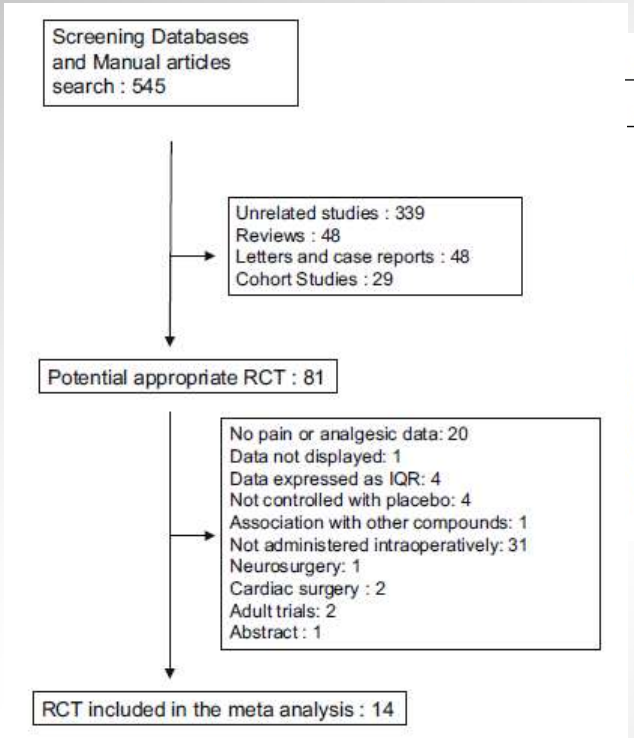
Induction au masque

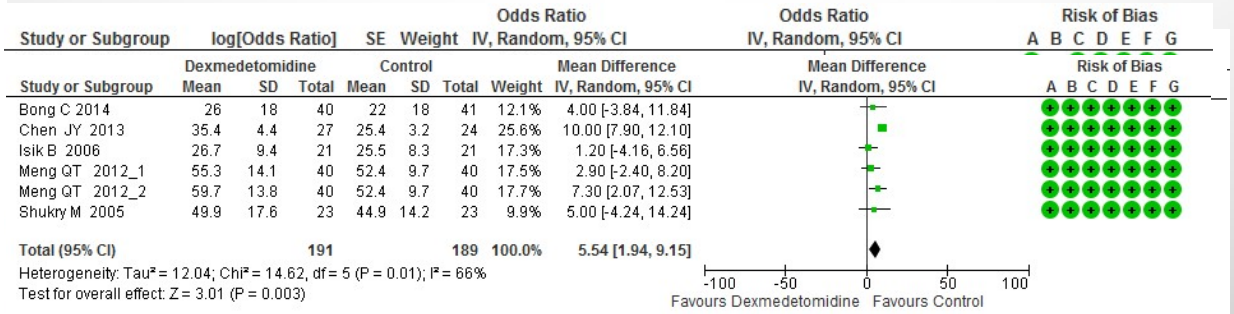
Séparation avec les parents

Jin JH et al. Can J Anaesth 2017.

Intraopératoire

Intraveineux: Bolus 0,3-2 $\mu g.Kg^{-1}$ Entretien 0-0,7 $\mu g.Kg^{-1}.h^{-1}$





Durée séjour SSPI

Bellon M et al. Pain Ther 2016.

Intraopératoire

- **Dexmedetomidine:**
  - **Bolus : 1 µg/Kg en 10 minutes**
  - **Entretien : 0,15 mg/Kg/h**
  - **Arrêt à la fermeture**

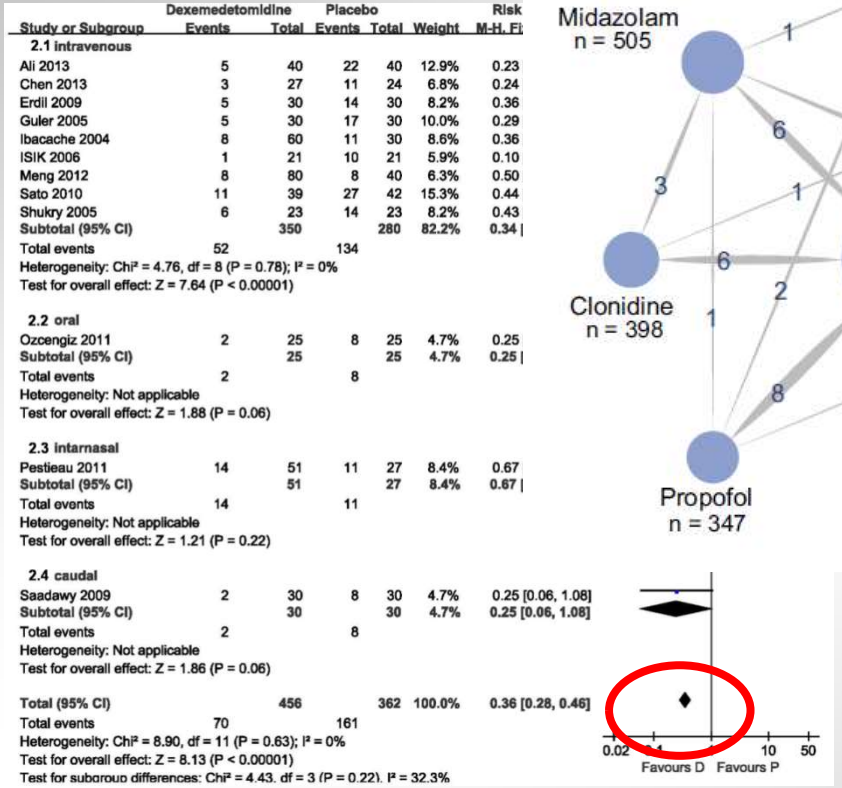
Aucun effet secondaire lié à d'utilisations (450 patients)

Techniques	Morphine J1 (mg/kg)	Morphine J3 (mg/kg)	Douleurs neuropathiques à 1 an
Contrôle (N = 33)	1,1 [0,6 – 1,54]	1,4 [0,5 – 2,3]	47.2 %
OFA: Dexmédetomindine & kétamine (N = 36)	**0,7 [0,2 – 1.5]**	**0,9 [0,07 – 1,9]**	**17.9 %**

Julien-Marsollier J et al. Pain Management 2021

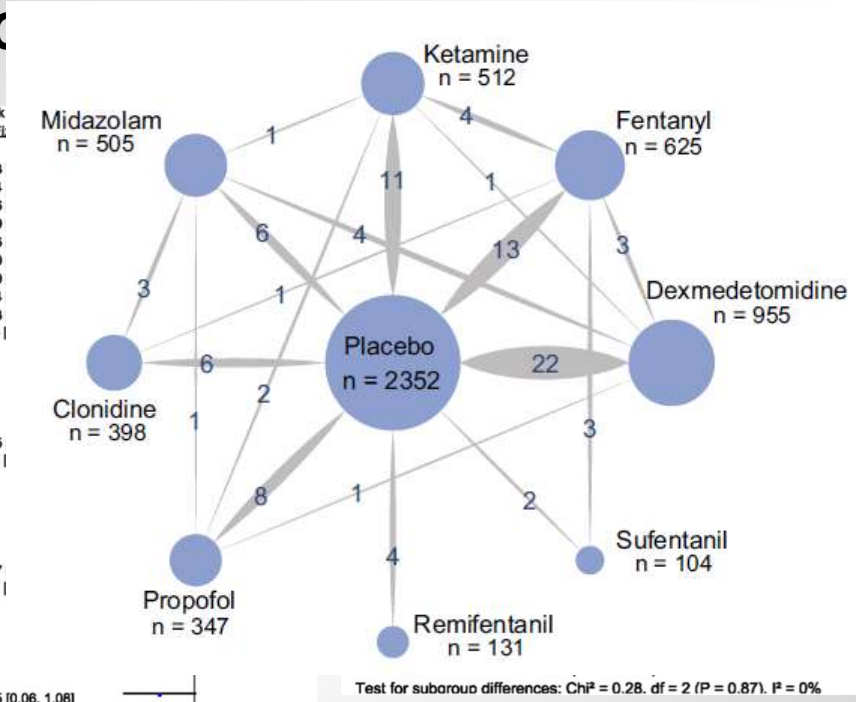
Intraopératoire

IV, Oral, IN: Bolus C



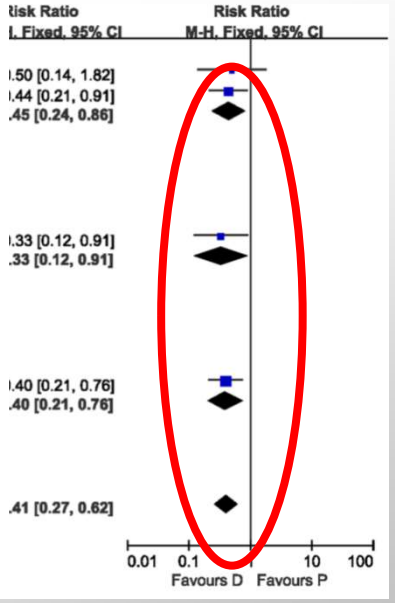
Study or Subgroup	Dexemedetomidine Events	Total	Placebo Events	Total	Weight	Risk M-H, Fi
2.1 intravenous						
Ali 2013	5	40	22	40	12.9%	0.23
Chen 2013	3	27	11	24	6.8%	0.24
Erdil 2009	5	30	14	30	8.2%	0.36
Guler 2005	5	30	17	30	10.0%	0.29
Ibacache 2004	8	60	11	30	8.6%	0.36
ISIK 2006	1	21	10	21	5.9%	0.10
Meng 2012	8	80	8	40	6.3%	0.50
Sato 2010	11	39	27	42	15.3%	0.44
Shukry 2005	6	23	14	23	8.2%	0.43
Subtotal (95% CI)		350		280	82.2%	0.34
Total events	52		134			
Heterogeneity: Chi² = 4.76, df = 8 (P = 0.78); I² = 0%						
Test for overall effect: Z = 7.64 (P < 0.00001)						
2.2 oral						
Ozcengiz 2011	2	25	8	25	4.7%	0.25
Subtotal (95% CI)		25		25	4.7%	0.25
Total events	2		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.88 (P = 0.06)						
2.3 intarnasal						
Pestieau 2011	14	51	11	27	8.4%	0.67
Subtotal (95% CI)		51		27	8.4%	0.67
Total events	14		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.21 (P = 0.22)						
2.4 caudal						
Saadawy 2009	2	30	8	30	4.7%	0.25 [0.06, 1.08]
Subtotal (95% CI)		30		30	4.7%	0.25 [0.06, 1.08]
Total events	2		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.86 (P = 0.06)						
Total (95% CI)		456		362	100.0%	0.36 [0.28, 0.46]
Total events	70		161			
Heterogeneity: Chi² = 8.90, df = 11 (P = 0.63); I² = 0%						
Test for overall effect: Z = 8.13 (P < 0.00001)						
Test for subgroup differences: Chi² = 4.43, df = 3 (P = 0.22), I² = 32.3%						

0.02 0.1 1 10 50
Favours D Favours P



Test for subgroup differences: Chi² = 0.28, df = 2 (P = 0.87), I² = 0%

.h⁻¹



Agitation au réveil

Ni J et al. Plos One 2015.
Wang X et al, Mol Neurobiol 2016

Sédation procédurale

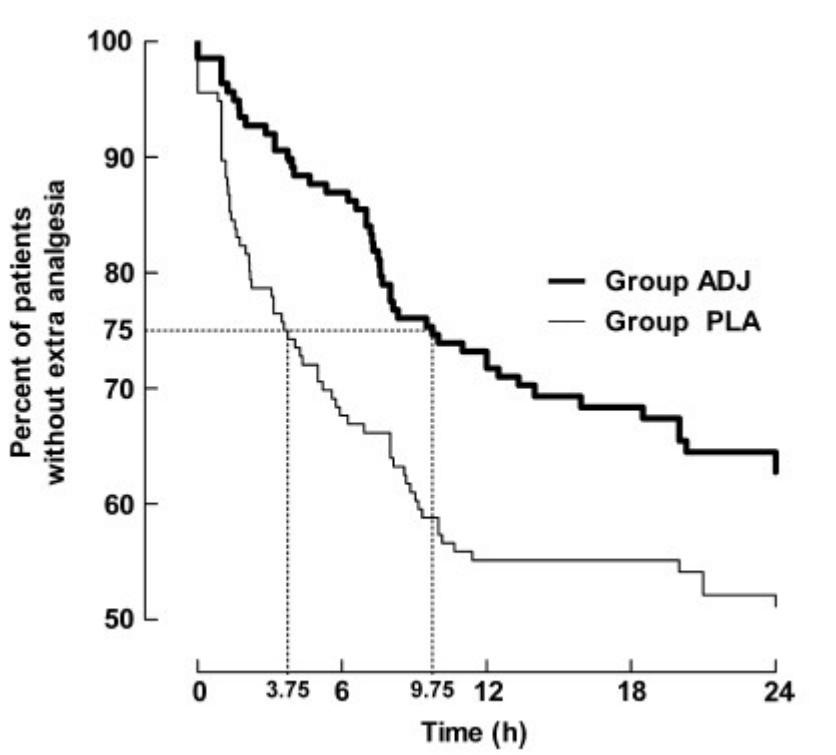
Auteurs	Age	Dex	Propofol	Endpoint Sédation correcte	Délais de sédations	Délais de réveil
Koroglu A et al 2006	1 à 7 ans	1 µg/ kg + 0,5 µg/kg/h	3 mg/kg + 0,1 mg/kg/h	Dex : 25/30 Pro: 27/30	Dex : 11 ± 4 mn Pro: 4 ± 2 mn	Dex : 27 ± 19 mn Pro : 27 ± 19 mn
Kamal K et al 2017 A	2 à 10 ans	2 µg/ kg + 1 µg/kg/h	1 mg/kg + 0,1 mg/kg/h	Dex: 30/30 Pro: 30/30	Dex : 7 ± 2 mn Pro: 3 ± 1 mn	Dex : 30 ± 5 mn Pro : 28 ± 6 mn

- Le truc pour que cela marche
  - Induction en salle d'induction
  - Dose de 2 µg/ kg + 1 µg/kg/h
  - Attendre que l'enfant dorme
  - Passage sur la table d'examen bolus de 1 mg/kg de propofol

Koroglu A et al. Anesth Analg 2006.
Kamal K et al, Saudi J Anaesth 2017

ALR

Clinical trial	Lundblad *et al.* 2015	Trifa *et al.* 2012	Trifa *et al.* 2010	Kaouech *et al.* 2008	Kaabachi *et al.* 2005
Peripheral block type	Ilioinguinal-iliohypogastric	Axillary brachial plexus	S		
No. of patients Adjunct/Plain	22/21	30/30	1		
Age (years)	1.7–7.9	1–8	0		
Weight (kg)	12–34	9–31	8		
Gender M/F	30/13	33/27	1		
Local anesthetic	Ropivacaine 0.2%	Ropivacaine 0.2%	E		
LA dose	0.2 ml·kg^{-1}	0.4 ml·kg^{-1}	0		
Adjunct	Dexmedetomidine	Clonidine	C		
Adjunct dose	0.3 mcg·kg^{-1}	1 mcg·kg^{-1}	1		
Pain scale (min-max)	CHIPPS/NRS (0–10)	CHEOPS (4–13)	0		
Trigger score for supplemental analgesia	≥4	>6	>		
Primary endpoint	Time to first administration of supplemental analgesia	Analgesia requirements during the first 24 h	T		



Lumblad M al. Curr Opin Anaesth 2016.
Lumblad M al. Pediat Anesth 2015.

ALR

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The European Society of Regional Anaesthesia and Pain Therapy/American Society of Regional Anesthesia and Pain Medicine Recommendations on Local Anesthetics and Adjuvants Dosage in Pediatric Regional Anesthesia

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- Dexmedetomidine has been used to prolong postoperative analgesia when used as an adjunct to neuraxial blocks (ie, caudal block). Because toxicity data are very limited in children, the dose used should be the minimally necessary to achieve the benefits and minimize potential adverse effects. (Evidence A2)

- Alpha-2 adrenoceptor agonists (eg, dexmedetomidine) can be used as an adjunct to prolong the duration of peripheral nerve blocks in children.[58] Because toxicity data are very limited in children, the dose used should be the minimally necessary to achieve the benefits and minimize potential adverse effects. (Evidence A1)

Conclusion

- **Clonidine:**
  - Utilisation comme prémédication pour la prévention de la DPO
  - Adjuvent de l'ALR
- **Dexmedetomidine**
  - Pas d'AMM
  - Utilisation plutôt en intraopératoire comme co-anesthéique et analgésique y compris pour la sédation
  - Epargne morphinique
  - Peur de recul pour l'ALR et particulièrement par voir médullaire en pédiatrie

39e CONGRÈS ANNUEL DE L'ADARPEF

Association des Anesthésistes Réanimateurs Pédiatriques d'Expression Française





Report des dates

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