Pharmacological Interventions for Remifentanil-Induced Hyperalgesia: A Systematic Review and Network Meta-Analysis of Preclinical Trials

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Background

To improve perioperative pain management, several interventions have been suggested for the prevention of increased pain sensitivity caused by opioids (called opioid-induced hyperalgesia). It is currently unclear which intervention is the most effective or appropriate in preventing opioid-induced hyperalgesia. Remifentanil is the most investigated opioid causing opioid-induced hyperalgesia.

Aim

To find the most effective intervention for remifentanil-induced hyperalgesia in preclinical trials

Method & Results

Systematic review

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62 studies

86 individual interventions and
6 combination interventions

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Studies evaluated for similarity to be included in the network meta-analysis

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Study groups analysed

	Plantar incision	Remifentanil characteristics	Animal model	QST	No of studies	No of interventions*
Group 1A	No	IV infusion of 1.0 µg/kg/min for 60 min	Male Sprague-Dawley rat	Von Frey	13	47
Group 1B	No	IV infusion of 1.0 µg/kg/min for 60 min	Male Sprague-Dawley rat	Hot plate	13	47
Group 2A	Yes	IV infusion of 1.0 µg/kg/min for 60 min	Male Sprague-Dawley rat	Von Frey	11	32
Group 2B	Yes	IV infusion of 1.0 µg/kg/min for 60 min	Male Sprague-Dawley rat	Hot plate	9	24
Group 2C	Yes	IV infusion of 1.0 µg/kg/min for 60 min	Male Sprague-Dawley rat	Radiant heat test	2	8
Group 3A	Yes	IV infusion of 1.2 µg/kg/min for 60 min	Male Sprague-Dawley rat	Von Frey	4	5
Group 3B	Yes	IV infusion of 1.2 µg/kg/min for 60 min	Male Sprague-Dawley rat	Radiant heat test	3	4
Group 4A	Yes	SC infusion of 0.04 mg/kg for 30 min	Male Sprague-Dawley rat	Von Frey	7	15
Group 4B	Yes	SC infusion of 0.04 mg/kg for 30 min	Male Sprague-Dawley rat	Radiant heat test	7	15
Group 5A	Yes	SC infusion of 0.04 mg/kg for 30 min	Male ICR mouse	Von Frey	2	10
Group 5B	Yes	SC infusion of 0.04 mg/kg for 30 min	Male ICR mouse	Hot plate	2	10

*includes different doses

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Most effective interventions

Best ranked intervention of the group
Anxa12-26 (500 µg)
MRS2179 (0.6 nmol/kg)
SIH (10 µg)
ANA-12 (180 nmol)
TDZD-8 (1 mg/kg)
Ketamine (10 µg)
Dexmedetomidine (50 µg/kg)
JWH015 (10 µg)
KN93 & ketamine (100 µg/kg & 2.1 mg/kg)
Ketamine (2.8 mg/kg)

All interventions

Investigated in 4 studies
Ketamine
MK-801
Ro25-6981
TDZD-8

Investigated in 3 studies
Hydrogen rich saline
KN93
Lidocaine
Naloxone / (+)-naloxone
PBN

Investigated in 2 studies
Naltrindole
Magnesium
Minocycline
PNU-120596
Ac-YVAD-CMK
Dexmedetomidine
Zeta inhibitory peptide

Investigated in 1 study
A438079
ACET
AgomiR-134
ANA-12
Anxa12-26
AMD3100
Amitriptyline
Artesunate
Betulinic acid
CAY10444
Chelerythrine
CLL1 neutralising antibody
CLL3 neutralising antibody
CLL7 neutralising antibody
CLL21 neutralising antibody
CLP257
CX3CR1 neutralising antibody
CXCL13 neutralising antibody
CYM-5442
CYM-5478
EphB1-Fc
EphB2-Fc
Dezocine
Deferoxamine
Dynamin-related protein 1 antisense oligos
FR167653
FTY720
Fz-8/Fc
Hevin-shRNA
HOE-140
IL-1ra
IL-17 antiserum
IL-18BP
IWP-2
JWH015
Kalirin-7 shRNA
LHVS
LiCl
LT1002
N-acetyl-cysteine
NASPM
NBI-74330
NMDA
NPC-15437
NS398
Maraviroc
Maropitant
MCC950
Methylnaltrexone
MPEP
MRS2179
Muscimol
PD98059
Philanthotoxin-7,4
PHA-543613
Roscovitine
Ru360
SB203580
SB225002
SC58125
SEW2871
SHPE
SIH
SK-1
TASP0277308
TNP-ATP
TMEM16C overexpression
TrkB/Fc
U0126
VEID-fmk

Combinations (investigated in 1 study)
Hydrogen-rich saline & Ro 25-6981
Hydrogen-rich saline & MK801
PHA-543613 & PNU-120596
Ketamine & KN93
CLP257 & Muscimol
Artesunate & MPEP

Conclusion

The current literature is too heterogeneous to produce a clear answer on which intervention is likely to be the most effective in preventing remifentanil-induced hyperalgesia. Future research in this field should prioritise finding the most effective intervention over testing the efficacy of new options. The results of our work can be used in planning which comparisons should be included in new trials.

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