Karolinska Institutet
Institutionen för Fysiologi och Farmakologi

Clonidine in Pediatric Anesthesia

Aspects on population pharmacokinetics, nasal administration and safety

Akademisk avhandling
som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i Rolf Luft L1:00 Karolinska Universitetssjukhuset Solna fredag 12 september 2014, kl 9.00 av

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Stockholm 2014

Abstract

Clonidine is widely use as premedication in pediatric patients and has many beneficial effects in the perioperative period. The introduction of population pharmacokinetics in the 1980s has proven useful when performing pharmacokinetic studies in children to circumvent previous limitations with traditional pharmacokinetics. The aim of the current thesis was to further study the pharmacokinetics (PK) and the pharmacodynamics (PD) of clonidine in the pediatric perioperative setting.

Population pharmacokinetics: In Study I PK-data after a clonidine bolus of 1-2 microg•kg^{-1} in 41 children were pooled with data from 4 published studies. A population PK analysis of clonidine time–concentration profiles was undertaken using nonlinear mixed effects modeling. The aim of this study was to clarify population PK in children. Clearance at birth was 3.8 l•h^{-1}•70 kg^{-1} and matured with a half-time of 25.7 weeks to reach 82% of the adult rate by 1 year of age. The relative bioavailability of epidural and rectal clonidine was unity (F = 1). In Study III the aim was to estimate the bioavailability of oral clonidine. Clonidine plasma concentrations in 8 children after oral clonidine 4 microg•kg^{-1} as premedication undergoing adenotonsillectomy were analysed. PK parameters were calculated using nonlinear effects mixed-effects models. Current data were pooled with data from 2 published intravenous studies. The oral bioavailability was found to be 55.4% (CV 6.4%; 95% CI 46.9-65.4%).

Nasal administration: In Study II the aim was to explore the absorption PK of clonidine nasal drops in children. Plasma levels from 9 children after clonidine administered as nasal drops 4 microg•kg^{-1} were analysed. Plasma PK following administration of clonidine nasal drops showed a considerable interindividual variability and absorption was delayed and limited.

A nasal aerosol increases the spread of the drug in the nasal cavity, thereby optimizing the possibility for enhanced and rapid absorption as well as circumventing any possible first-pass effects that can be associated with oral drug administration. In Study IV the onset time of preoperative sedation after clonidine administered as a nasal aerosol was evaluated using a prospective, randomized, double-blind, controlled design including 60 patients receiving placebo, 3-4 microg•kg^{-1} or 7-8 microg•kg^{-1} respectively. At 45 min, adequate sedation was seen in 65% of the patients in both clonidine groups.

Safety: One of few limitations with clonidine is its association with reduced heart rate. The aim of Study V was to investigate the incidence of bradycardia in children premedicated with either oral or intravenous clonidine as compared to children not receiving pharmacologic premedication. On arrival to the operating room heart rate was recorded. 1 507 patients were included in the analysis of which 685 patients did not receive any premedication (Group 0), 305 patients received iv Clonidine (Group CIV) and 517 patients were given oral Clonidine (Group CPO). 1 in Group 0 (0.15%; 95% CI: 0-0.81%), 0 in Group CIV (0%; 95% CI: 0.00-0.98%) and 5 patients in Group CPO (0.97%; 95% CI: 0.31-2.24%) were observed to have a HR of < 85% of the 1st centile.

Conclusions: Clearance is reduced in neonates and infants. It is recommended to reduce the doses of clonidine in this age-group. Oral bioavailability of clonidine in children is reduced as compared to adults. Our results suggest that it would be necessary to administer at least twice the intravenous dose orally to get a similar effect of clonidine in children when compared with intravenous administration. The absorption of clonidine as nasal drops is low and clonidine administered as a nasal aerosol did not improve the onset time of preoperative sedation. Nasal administration of clonidine as drops or aerosol cannot be recommended if an onset time ≤ 30 min is desired. The incidence of bradycardia following premedication with clonidine in a pediatric population is very low. Hence it does not appear rational to refrain from using clonidine as premedication in children only due to the potential risk for bradycardia.

ISBN 978-91-7549-629-0