Diclofenac Pharmacokinetics and Dose Recommendations for Children aged 1-12

Diclofenac, a non-steroidal anti-inflammatory drug (NSAID), underwent pharmacokinetic meta-analysis for dose recommendation in children aged 1-12 years.

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February 14, 2011– A meta-analysis of children aged 1-12 years has concluded that single doses of 0.3 mg.kg⁻¹ for intravenous, 0.5 mg.kg⁻¹ for suppositories, and 1 mg.kg⁻¹ for oral diclofenac yield a similar concentration–time curve (AUC) as a 50 mg dose in adults.

Joseph F. Standing, Ph.D., with the Department of Pharmaceutical Biosciences, Uppsala University, in Sweden, and colleagues reported their findings in the January 30, 2011, issue of Pediatric Anesthesia.

According to the researchers, it is well recognized that diclofenac is an effective analgesic for postoperative pain in children. “Through pooled pharmacokinetic analysis, this study has clarified the appropriate dose for parenteral, oral, and rectal administration,” they note.

Recently, a Cochrane review established a major knowledge gap in diclofenac use in dosing information. The current pharmacokinetic meta-analysis was undertaken to determine the recommended dose of diclofenac for children aged 1–12 years.

Studies containing diclofenac pharmacokinetic data were identified through a Cochrane systematic review. Authors were asked to provide raw data from these studies.

A pooled population analysis was undertaken in NONMEM (non-linear mixed effect modeling software package) to define the pharmacokinetics of intravenous, rectal and oral diclofenac in children. Simulations were performed to produce a comparable area under the diclofenac concentration–time curve (AUC) to that of a 50-mg dispersible tablet in adults.

Data from 111 children was analyzed. This data consisted of 375 samples following intravenous, oral suspension, and suppository use. Adult dispersible tablet and suspension data were added to provide a reference AUC and support the absorption modeling, respectively.

A three-compartment model described disposition, a dual-absorption compartment model was used for suspension and dispersible tablet data, and a single-absorption compartment model was used for suppositories.

According to the researchers, “A major finding of this study was that rectal bioavailability of diclofenac is almost twice that of oral diclofenac.” The estimate of clearance was 16.5 l•h⁻¹•70-1 kg and bioavailabilities were 0.36, 0.63, and 0.35 for suspension, suppository, and dispersible tablets, respectively.

The researchers explain, “This is probably because of the high pH in the rectum allowing for efficient drug dissolution and that the middle and inferior rectal veins bypass the liver, meaning diclofenac undergoes less extensive first-pass metabolism by this route.”

“In light of these meta-analysis data and given the present state of our knowledge on NSAID pharmacology, it seems reasonable to assume that the pharmacokinetic/pharmacodynamic relationship is similar in adults and children aged 1–12,” the researchers note.
Dr. Standing received postdoctoral funding from Pfizer. Jeff Rothwell of Rosemont Pharmaceuticals Ltd provided the adult bioequivalence data.