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TITLE: THE PHARMACOKINETICS AND PHARMACODYNAMICS OF MINAXOLONE

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Introduction. Minaxolone is a new water-soluble intravenous steroid anaesthetic. Early clinical reports^{1,2,3} indicate that it is an effective induction agent producing minimal cardiorespiratory depression. The anaesthetic action appears to be longer than Thiopentone, Methohexitone and Alfathesin. Recovery, while initially longer than that of other induction agents, is remarkable for its completeness and lack of hangover. There appears to be a lack of cumulative effect from repeated doses. The purpose of this study was to assess the pharmacokinetics and pharmacodynamics of Minaxolone in patients, and was undertaken in conjunction with the previously reported clinical evaluation³.

Methods. Fifteen healthy female patients undergoing minor gynaecological procedures were studied. Institutional approval of the protocol was given and an informed written consent was obtained from all patients. Anaesthesia was induced with a Minaxolone infusion which was continued until the eyelash reflex was lost, and was maintained with 70% nitrous oxide and standard Minaxolone increments if clinically indicated. Blood samples were taken from a cannula inserted into the antecubital fossa opposite to the site of administration, and were taken at set intervals from 4 to 180 minutes following induction. Plasma was separated and stored frozen until assayed. Minaxolone levels were determined using a sensitive gas chromatographic method utilizing a nitrogen specific detector. Nine patients received only the induction dose of Minaxolone, while six patients received at least one additional increment. Pharmacokinetic parameters were estimated from those patients receiving a single dose of Minaxolone. Recovery times were assessed from the time of termination of anaesthesia until the patient could first recall her date of birth.

Results. (a) **Pharmacokinetics.** Inspection of the semilogarithmic plots of plasma Minaxolone level and time suggested that plasma levels followed a biexponential two compartmental first order decay. This model was therefore assumed and a 'best fit' biexponential curve obtained for each patient using a least squares non-linear regression computer programme⁴ without weighting. Mean ages and weights in the patients studied were 22.8 years and 59.8 kg respectively. The average induction dose of Minaxolone was 54.7 mg. Mean distribution volume

(V^{β}) was 1.59 l.kg⁻¹. $T_{1/2}^{\alpha}$ was 2.1 minutes and $T_{1/2}^{\beta}$ was 47.2 minutes. Total plasma clearance was 1.55 l.min⁻¹. (b) **Pharmacodynamics.** Mean plasma levels of Minaxolone at recovery were 265 $\mu\text{g.ml}^{-1}$ (± 81.4) in patients receiving one dose of Minaxolone and 236 $\mu\text{g.ml}^{-1}$ (± 66.0) in patients receiving two or more doses of Minaxolone. Recovery times for these two groups of patients were 24.4 minutes and 32.9 minutes respectively. Mean plasma levels of Minaxolone at two and three hours after induction were 77 and 56 $\mu\text{g.ml}^{-1}$ respectively. There was no significant correlation between plasma Minaxolone level and changes in cardiorespiratory variables measured.

Conclusion. The decay of Minaxolone in plasma followed two compartmental first-order kinetics. Both distribution and elimination were rapid. Plasma clearance of Minaxolone was 1.55 l.min⁻¹, suggesting either that the liver totally clears Minaxolone not only from plasma but also from red cells, or that hepatic degradation alone cannot entirely account for its elimination. The similarity of plasma levels at recovery for patients receiving single and multiple doses of Minaxolone suggests a valid relationship between plasma level and effect. The pharmacokinetics and pharmacodynamics of Minaxolone as determined in this study indicate that it may be a useful induction agent which should also be suitable for administration by continuous infusion.

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