Indoprofen, a non-steroidal anti-inflammatory analgesic which does not depress respiration in normal man

A study comparing indoprofen with morphine


Summary

The respiratory effects of intravenous indoprofen 400 mg, a highly effective non-steroidal anti-inflammatory analgesic, were compared with those of morphine 10 mg in 10 healthy volunteers. Morphine exhibited its characteristic adverse respiratory depressant properties. Indoprofen, in contrast, did not influence the subjects' breathing pattern.

Subjects and methods

Ten healthy subjects (7 men and 3 women) were studied with their informed consent. They were randomly divided into two groups; 8 received indoprofen and 2 morphine sulphate. The mean ages and weights were 20.2 years (range 16 - 22 years) and 67.5 kg (range 53 - 90 kg) respectively. The study was approved by the Ethics and Standards Subcommittee of the Faculty of Medicine of the University of Natal, and the Medicines Control Council of South Africa.

The subjects were studied lying supine in a quiet laboratory. Each subject fasted for 4 hours before the study, and emptied his or her bladder immediately before entering the laboratory. An intravenous infusion of normal saline was established in the left arm and maintained at the rate of 150 - 200 ml/h. An extension on the intravenous line was used so that the injection port and infusion bag were outside the line of vision of the subject. After the establishment of the intravenous line, the subject lay on a couch and breathed room air through a non-rebreathing apparatus which measured and recorded end-tidal PCO2.

End-tidal PCO2 and respiratory rate were measured using a Hewlett Packard Capnometer 47210A. The analogue signals from this instrument were recorded on a Beckman Dynagraph via a 30-second time constant signal conditioner to give a volume signal. The volume signals were summed and displayed against time, thus giving a measurement of minute volume. This device was automatically reset after a predetermined volume. The capnometer was calibrated on its internal calibration system and was checked against a gas of known CO2 concentration.

The differential pressure across a No. 2 Fleisch pneumotachograph was measured by a Statham differential pressure transducer. This analogue signal was integrated with respect to time to give a volume signal. The volume signals were summed and displayed against time, thus giving a measurement of minute volume. This device was automatically reset after a predetermined volume. The pneumotachograph was calibrated using a positive displacement rigid spirometer.

The subjects inhaled room air and then exhaled, first through the in-line detection head of the capnometer and subsequently through the pneumotachograph. Air flow was controlled by an ultra-low resistance J valve, acting as a non-rebreathing valve, and a face mask with a pneumatic cuff to ensure an airtight seal against the skin.

A period of 15 - 20 minutes of quiet breathing was allowed for the subject to become accustomed to the apparatus. When the measured variables had stabilized, indoprofen 400 mg or morphine 10 mg in 10 ml sterile water was injected slowly (over 5 minutes). The end-tidal PCO2 and minute volumes were then recorded continuously for the following 50 minutes.

From these recordings numeric values for minute volume and end-tidal PCO2 at 5-minute intervals were obtained. The mean and SEM for each set of readings were calculated.
The arm used for intravenous infusion and drug injection was inspected on the second day for signs and symptoms of thrombophlebitis.

**Results**

End-tidal Pco₂ and minute volumes, before (-15 and 0 minutes) and after (15, 30 and 45 minutes) injection of each drug are shown in Figs 1 and 2. There was no significant change in either end-tidal Pco₂ or minute volumes after injection of indoprofen. However, end-tidal Pco₂ levels rose (P < 0.10) and minute volumes decreased (P < 0.01) significantly following injection of morphine sulphate (Student's t-test).

After the injection of indoprofen, 3 out of 8 subjects complained of slight discomfort in the arm, but none had severe pain or any systemic effects. No thrombophlebitis was seen later.

Fig. 1. Mean changes in end-tidal Pco₂ (--- morphine; ... --- indoprofen).

**Discussion**

In 1973 Nannini *et al.* reported that new iso-indole derivatives were highly active in experimental animals, both as analgesics and anti-inflammatory agents. One of the most promising derivatives isolated was indoprofen. Indoprofen is a weak acid with a relatively low pKa and should therefore theoretically circulate in the blood mainly in the ionized form and not cross the blood-brain barrier in significant amounts. Furthermore, indoprofen is rapidly eliminated from the body within- and between-patient comparisons, have shown indoprofen to have a significant analgesic activity in the treatment of a wide range of painful conditions. In double-blind studies indoprofen compared favourably with pentazocine in 70 patients with severe biliary colic pain and with pethidine in 80 patients with postoperative pain.

In this study, indoprofen produced no change in ventilatory parameters while morphine sulphate caused a statistically significant depression of minute ventilation. Should indoprofen prove satisfactory as an analgesic in anaesthetic practice, the drug may well prove to be the drug of choice for the relief of pain in the postoperative period, especially in patients whose respiratory function is already compromised.

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**REFERENCES**