The analgesic and respiratory depressant activities of *N*-allyl noretorphine and morphine in the mouse

It is generally accepted that equally analgesic doses of all narcotic analgesics are accompanied by the same degree of respiratory depression. No narcotic analgesic would seem preferable to morphine in this respect. Even the narcotic antagonist analgesics like pentazocine depress respiration to the same extent as will equi-analgesic doses of narcotic analgesics (Dyrberg, Henningsen & Johansen, 1967).

The recent report by Blane, Boura & others (1968) that the *N*-allyl derivative of noretorphine (R & S 218-M) showed a dissociation between analgesia and respiratory depression was thus of interest. The published evidence upon which this claim was made did not include experiments in which analgesia and respiration in the same animal were measured concurrently. We have now examined the analgesic and respiratory depressant activities of 218-M and compared it with morphine.

Groups of not less than six mice were used. Drugs were administered intraperitoneally in a volume of about 0·3 ml/25 g mouse. Dilutions, where necessary, were made in saline. In each experiment a control group treated with an equal volume of saline was investigated concurrently. Analgesia was estimated by the hot plate technique—the temperature of the plate being 55° and the end point taken as a shaking movement of a hind limb (Beecher, 1957). Respiratory rate was measured by placing the mouse's snout into the barrel of a syringe connected to a pressure transducer the output of which was recorded on a pen recorder.

Respiratory movements were recorded for at least 10 s then hot plate reaction time was determined. A full investigation of time course of drug action was made in each experiment—measurements being made at either 15 or 30 min intervals. The two parameters were investigated until they did not differ from those seen in the concurrently investigated controls.

Hot plate reaction time is expressed as the difference between the mean hot plate reaction time in a drug-treated group and the mean of the concurrently investigated control group. Depression of respiratory rate is calculated as the difference between the mean respiratory rate in a drug-treated group and that in its control, expressed as a percentage.

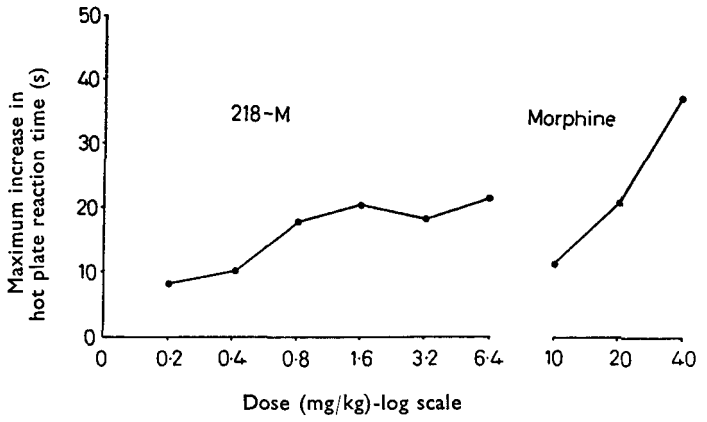

FIG. 1. The relation between the maximum increase in hot plate reaction time(s) and log dose for 218-M and morphine. Each point represents the mean based upon observations in not less than 12 and not more than 30 mice.

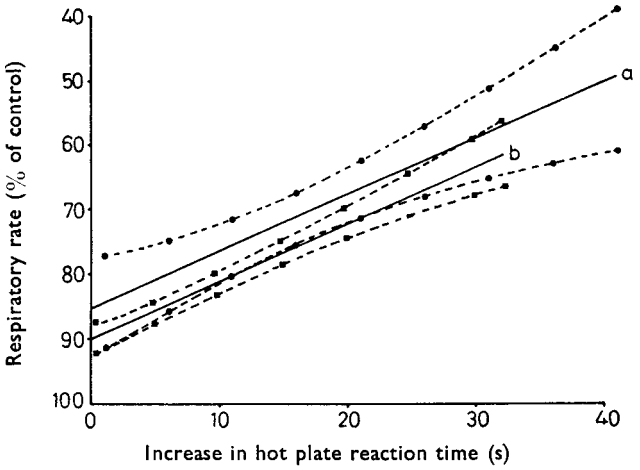

FIG. 2. The regression lines relating increase in hot plate reaction time to depression of respiratory rate for morphine (a) and 218-M (b). The broken lines about each regression line represent the 95% confidence limits for morphine (- - - ● - - -) and 218-M (- - - ■ - - -).

Fig. 1 shows the log dose response curves for morphine and 218-M for maximum increase in hot plate reaction time. Increasing the dose of 218-M from 0·8 to 6·4 mg/kg produced a negligible increase in reaction time. On the other hand doubling the equi-analgesic dose of morphine from 20 to 40 mg/kg produced a marked increase in reaction time. The maximum effect of morphine was not determined because of causing tissue damage during the long exposure of the mice to the hotplate. 218-M therefore has a lower peak effect than has morphine in our experiments.

Fig. 2 relates the degree of analgesia to the concurrent depression of respiratory rate produced by morphine and 218-M at all the various dose levels and intervals after injection. The relation between analgesia and respiratory depression is expressed as a regression line based upon 102 mean observations (218-M) and 42 mean observations (morphine). The intercepts for the regression lines for 218-M and morphine were 90·49 and 85·64% of control respiratory rate. The slopes for 218-M and morphine were 0·92 and 0·89 respectively. The 95% confidence limits for each regression line are included. There is no significant difference ($P > 0{\cdot}5$) between the two slopes.

These results indicate that there is little dissociation between the analgesic and respiratory depressant effects of 218-M in the mouse as measured by our technique, and that this drug has a lower peak effect than has morphine.

Blane, Boura & others (1968) state that 218-M has a lower peak depressant effect on respiratory rate than has morphine, but for analgesia the log dose response curves are parallel. Amongst the extensive evidence presented by these authors, it is stated that the potency ratio for analgesia in mice compared with morphine is 131 to 1, but for respiratory rate depression is about 0·5 to 1. The standard for analgesia which they used—their ED50—was the dose to increase hot plate reaction time by 100% in 50% of the mice (personal communication). This is a relatively low dose, for in our experiments, in which control reaction time was about 5 s, an increase of 5 s is at the bottom end of our log dose response curve (Fig. 1). On the other hand their standard for respiratory depression from which their potency ratio was calculated was the dose to depress respiratory rate by 50%. This is a relatively enormous dose—indeed we infrequently saw rate depression of this magnitude. Thus the potency ratio for analgesia was established at one extreme end of the log dose response curves and that for rate depression at the other. To interpret the results obtained

in this way as indicating dissociation between analgesia and respiratory depression relies on the two drugs having log dose response curves which are identical with respect to slope and maximum. We were unable to confirm that morphine and 218-M share these characteristics in the mouse.

We wish to express our thanks to Reckitt and Sons Ltd of Hull for the sample of 218-M.

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REFERENCES

BEECHER, H. K. (1957). *Pharmac. Rev.*, **9**, 59–209.

BLANE, G. F., BOURA, A. L. A., LEACH, E. C., GRAY, W. D. & OSTENBERG, A. C. (1968). *J. Pharm. Pharmac.*, **20**, 796–798.

DYRBERG, V., HENNINGSEN, P. & JOHANSEN, S. H. (1967). *Acta anaesth. scand.*, **11**, 77–84.

An improved method of filtration in the determination of morphine by precipitation with fluorodinitrobenzene

In the high ambient temperatures (70–90° F) frequently encountered during the Australian summer, the method for the determination of morphine described by Garratt, Johnson & Lloyd (1957) and Garratt (1964), in which the dinitrophenyl ether is precipitated with 1-fluoro-2,4-dinitrobenzene, is difficult to carry out because of the increased solubility of the precipitate as the solution warms up during filtration. The transference of the precipitate to the filter crucible is made more difficult by the loss of liquid through evaporation.

To overcome these difficulties, the precipitation of the dinitrophenylether is effected in a pear-shaped flask (Quickfit & Quartz FP 50/1) maintained at 60° F in a constant-temperature water bath. When precipitation is complete, the supernatant liquid is drawn off by vacuum through an Emich filter stick with a porosity 3 sintered glass disc and the flask and precipitate are then washed with 4 × 2 ml portions of acetone cooled to 60° F.

In this way precipitation and filtration are carried out at 60° F and there is no troublesome transference of precipitate to the filter. The use of a pear-shaped flask facilitates washing of the precipitate since there is little dead volume, but it is necessary to dry the flask with the filter and precipitate in a vacuum oven to remove all traces of acetone.

The Emich filter stick is made by fusing a porosity 3 sintered glass disc (8 mm diameter × 2 mm thick) to the flared end of a Pyrex tube (1·5 mm i.d. and 4 mm o.d.), the overall length being approximately 14 cm.

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REFERENCES

GARRATT, D. C., JOHNSON, C. A., & LLOYD, C. J. (1957). *J. Pharm. Pharmac.*, **9**, 914–927.

GARRATT, D. C., *The Quantitative Analysis of Drugs*, 3rd Edn, p. 480, London: Chapman and Hall.