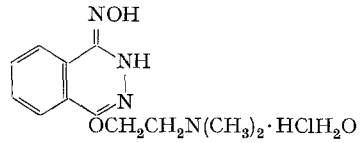
## Investigations Into the Site of Action of Taloximine: A New Respiratory Stimulant Molecule

Taloximine is a phthalazine derivative with the structure:




The general chemical properties of phthalazines have been described by PARSONS and TURNER[1]. Taloximine has been shown to be a highly effective respiratory stimulant in the rabbit and a bronchodilator in the rat and guinea-pig[2].

The present investigation was undertaken to determine, firstly, whether taloximine stimulated respiration by direct action on the respiratory centre or whether it acted through peripheral chemoreceptors and, secondly, should its respiratory action be shown to be peripheral, whether any action of taloximine on the central nervous system could be demonstrated.

Cats, lightly anaesthetized with sodium pentobarbitone (20 mg/kg i.p.), were used. The tracheae were cannulated and cannulae were inserted into the jugular veins. Respiration was recorded by a Greer manometer which recorded the pressure drop across a gauze resistance connected across the tracheal cannula. The output of the manometer circuit was displayed on a Tektronix 502A oscilloscope. Integration of the pressure changes over 10 sec intervals gave an arbitrary indication of ventilatory volume, and this trace was fed into the lower beam of the oscilloscope.

20 mg/kg of taloximine given i.v. increased both the rate and depth of respiration; effects were maximal 1 min after injection, and some increase persisted up to 10 min after injection (Figures 1–3). After denervation of the carotid body and division of the vagi and recurrent laryngeal nerves, injections of 20 mg/kg of taloximine i.v. caused a short-lived depression of respiration (Figures 1–3), but injection of a larger dose of taloximine (40 mg/kg i.v.) gave rise to respiratory stimulation (Figure 1c).

A comparison was made between the effect of denervation of the chemoreceptors on the respiratory stimulatory action of taloximine and on the action of 2 other respiratory stimulants, viz. bemegride (Megimide, Nicholas Laboratories) and nikethamide (Leptazol, Ciba). Bemegride (8 mg/kg i.v.) was effective as a respiratory stimulant both before and after denervation of the chemoreceptors but after denervation this effect was less prolonged (Figure 3). Nikethamide (100 mg/kg i.v.), like taloximine, was an effective respiratory stimulant before denervation of the chemoreceptors and, like taloximine, caused depression of respiration after denervation. These results, therefore, coincide with the known pharmacology of bemegride and nikethamide[3] and indicate that the mode of action of taloximine resembles that of nikethamide but that taloximine is effective at a much smaller dose in terms of mg/kg.

It was therefore shown that it was necessary for the peripheral chemoreceptor reflexes to be intact for a dose of 20 mg/kg of taloximine to stimulate respiration, but this did not necessarily imply that taloximine had a direct action upon these reflexes, especially as it had also been demonstrated that 40 mg/kg doses of taloximine could act after denervation of the reflexogenic chemoreceptor areas. Recordings from the carotid body nerves

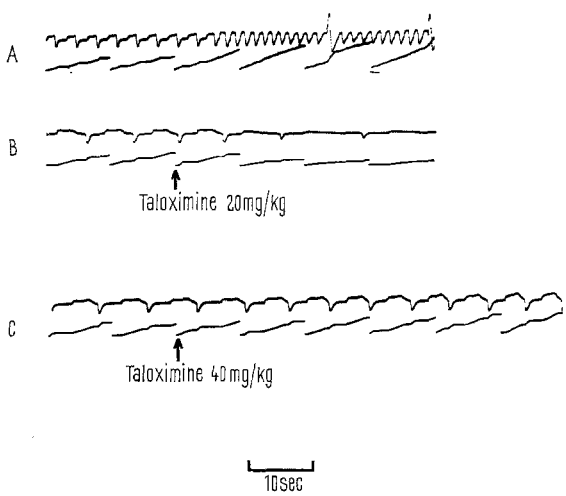



Fig. 1. (A) Response of barbiturate anaesthetized cat with chemoreceptor areas intact to 20 mg/kg of taloximine i.v. (B) Response of same cat to 20 mg/kg taloximine i.v. after denervation of carotid body and aortic chemoreceptors. (C) Response of same cat to 40 mg/kg taloximine i.v. after denervation of chemoreceptors.

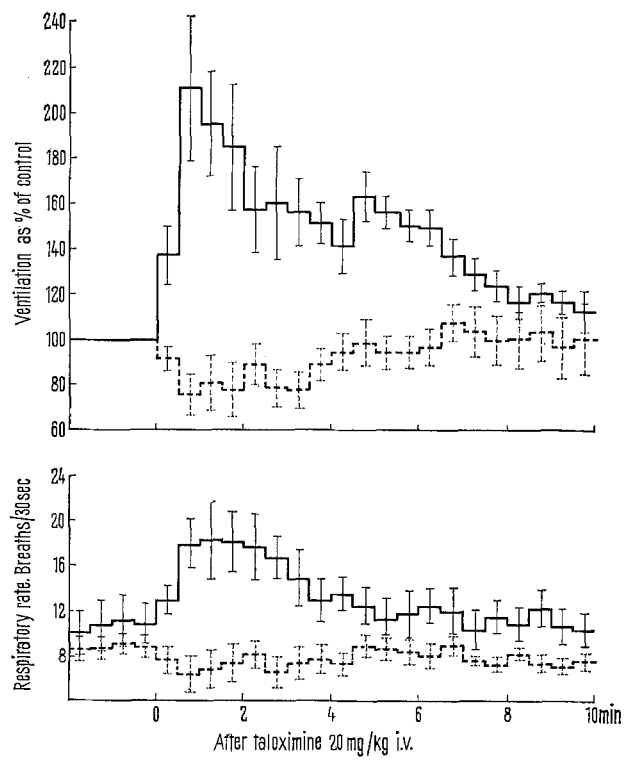



Fig. 2. (*above*) Showing change in ventilation as percentage of control to 20 mg/kg taloximine i.v. solid line, before denervation of chemoreceptors; interrupted line, after denervation of chemoreceptors. (*below*) Showing change in respiratory rate in response to 20 mg/kg taloximine i.v. before and after denervation of chemoreceptors. All data shown are the mean from 9 cats ± S.E.

[1] D. G. PARSONS and A. F. TURNER, Pat. Specification No. 1,094,044 (1967).
[2] M. DALY, J. E. LIGHTOWLER and R. W. PICKERING, Br. J. Pharmac. *35*, 283 (1969).
[3] L. S. GOODMAN and A. GILMAN, *Pharmacological Basis of Therapeutics*, 3rd edn (MacMillan, New York 1965), p. 350.

were taken, and increased frequency of discharge in filaments of these preparations were observed following i.v. administration of taloximine. The electroneurograms were taken from multifilament preparations and could not be expressed in a quantitative manner. This supports the other data indicating that taloximine has a direct action on peripheral chemoreceptors.

appears that the dose that caused respiratory stimulation after reflexogenic area denervation was close to the convulsive dose.

It can be concluded that taloximine acts as a respiratory stimulant predominantly by its actions on the reflexogenic areas, but it also has central nervous actions amongst its pharmacological activities.

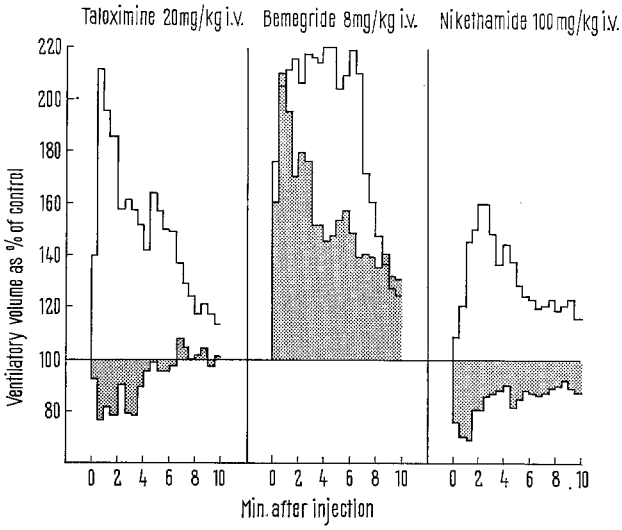



Fig. 3. Responses of 9 barbiturate anaesthetized cats to taloximine, bemegride and nikethamide given i.v. before denervation of the chemoreceptors (open histogram), and after denervation of the chemoreceptors (stippled histogram).

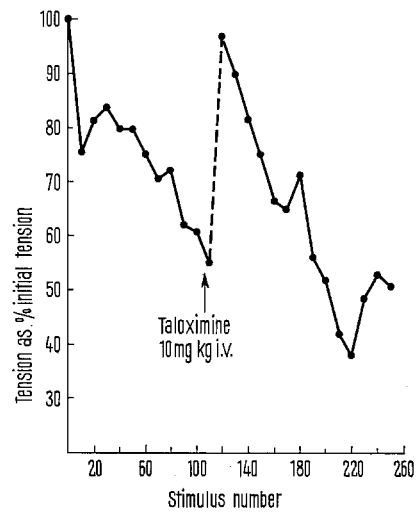



Fig. 4. Enhancement of the flexor withdrawal reflex in the decerebrate spincal cat preparation against a background of response decrement due to habituation following an i.v. dose of 10 mg/kg taloximine.

In view of the observations that large doses of taloximine stimulated respiration after denervation of the chemoreceptors it was decided to determine whether taloximine was effective in promoting some other parameter of central nervous system activity. The effect of taloximine on the flexor withdrawal reflexes was, therefore, examined in the decerebrate spinal cat preparation described by GRIFFIN and PEARSON[4]. In this preparation the isometric tension recorded from a slip of the biceps femoris muscle was measured in response to repeated application of uniform electrical stimuli to the ipsilateral hindpaw. Application of such stimuli results in a progressive decrement of the flexor response.

Enhancement of the flexor withdrawal reflex against a background of response decrement due to habituation was shown to occur with a dose of 10 mg/kg i.v. of taloximine (see Figure 4). Despite this enhancement of the flexor reflex at doses as low as 10 mg/kg i.v. taloximine was not shown to cause convulsions in the cat until doses in excess of 40 mg/kg were given. It therefore

*Résumé.* Une substance nouvelle, la taloximine, administrée par voie intraveineuse produit chez le chat à une dose de 20 mg/kg indemne une augmentation de l'effort respiratoire. On montre qu'à cette dose la taloximine accélère la fréquence des décharges enregistrées à partir de filaments multifibrillaires du nerf du corps carotidien.

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[4] J. P. GRIFFIN and J. A. PEARSON, Brain Res. *8*, 185 (1968).
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## The Influence of β-Methasone on Antimicrobial Activity of Gentamicin

It is uniformly accepted that corticosteroids in high concentrations decrease metabolic functions. In certain low concentrations, however, they increase oxygen consumption of human and animal cells, as has been demonstrated in cell culture experiments; suspensions of microorganisms (bacteria and fungi in resting and proliferating phase) reveal an activated cell metabolism in the presence of corticosteroids in low concentrations, too [1–3]. For this reason, an inhibition of antimicrobial effects of antibacterial agents might occur when used

[1] W. RAAB and J. WINDISCH, Arch. klin. exp. Derm. *233*, 363 (1969).
[2] W. RAAB, Arch. klin. exp. Derm. *228*, 71 (1967).
[3] W. RAAB, Arch. klin. exp. Derm. *231*, 250 (1968).