A NOTE ON BENZYLPENICILLIN DIETHYLAMINOETHYL ESTER

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The diethylaminoethyl ester of benzylpenicillin (PDE) differs from other benzylpenicillin derivatives, in that it has a pronounced affinity for lung tissue.[1] It is used clinically in the form of the hydriodide.* As a carboxylic acid ester of an amino-alcohol it might be expected to have some pharmacological activity.

The physico-chemical properties, in particular the solubility and rate of hydrolysis, will be described in detail elsewhere (Juhl Nielsen *et al.*[2]). In 0·9 per cent. sodium chloride solution at *p*H 7·3 and 37° C. it undergoes 50 per cent. hydrolysis within 23 minutes to form penicillin and diethylaminoethanol. Control experiments have shown that the pharmacological activity of the hydrolysis products in equimolar amounts is not detectable at the levels used in this work. The effects depend greatly on the mode of administration and the salt used, the hydriodide is sparingly soluble while the hydrochloride is highly soluble in aqueous solution.

Oral administration. The hydrochloride and hydriodide are slowly absorbed and partly hydrolysed in the gastrointestinal tract. Consequently after oral administration, blood levels are low and toxic effects are only seen with extremely high doses.

Parenteral administration. The slightly soluble hydriodide is less toxic than the highly soluble hydrochloride. In mice, rats and rabbits the LD50 (subcutaneous administration) is the same for these species: about 2000 mg. per kg. and about 1500 mg. per kg. for the hydriodide and hydrochloride respectively. The effects of intravenous administration were investigated with the more soluble hydrochloride. In the rat, mouse and rabbit the LD50 was found to be approximately 20 to 40 mg. of the hydrochloride per kg. (injection time, 5 seconds). Death occurs within a few seconds after intravenous injection with clonic and tonic convulsions. A pharmacological investigation has been undertaken to determine the cause of death.

Circulatory and respiratory effects. Intravenous injection of 10 mg. of the hydrochloride per kg. (rabbit, urethane) produces a sudden drop in arterial blood pressure and changes in the electrocardiogram. Depressive effects were shown on the conducting system, first the sino-auricular node and thereafter the auriculo-ventricular node. The effect is temporary and circulatory function is rapidly restored. Higher doses may lead to complete cardiac arrest, respiratory failure and death. Intravenous administration could not be used in studies on respiration because of the speed with which the animals recovered (or died) after injection. The effects on respiration were investigated after intramuscular injection

* "Leocillin" (Denmark), "Estopen" (England).

(rabbit, urethane). Large doses, about 1 g. of the hydrochloride per kg., gave rise to symptoms similar to those observed after intravenous injection but the course of events was slowed enabling more detailed studies to be made. The first effect is a drop in arterial blood pressure, at this time respiration is unaffected or slightly stimulated. Failure of respiration does not occur until immediately before death when the blood pressure has fallen to zero. The main toxic effect is therefore on the circulation. The anoxia consequently produced may explain the respiratory depression seen in anæsthetised animals and the convulsions noted in unanæsthetised animals.

The action on the circulation could be caused by either a central or a peripheral effect. A primary central effect is probably excluded by the observations that injection into the carotid artery does not cause a depression of blood pressure while intravenous injection into the spinal rabbit is immediately followed by depression of blood pressure.

Isolated heart. A Ringer-perfused rabbit heart was employed. Benzylpenicillin diethylaminoethyl ester at a concentration of 10 μg./ml. caused distinct inhibition of contraction while 100 μg./ml. completely arrested contraction.

Isolated rabbit ear. Addition to the Ringer perfusion fluid caused no changes in the vascular tone. Yet, a possible inhibition of the normal tone (controlled by the autonomic system) will not be observed in experiments with an isolated vascular bed. Therefore, the experiments are not conclusive. However, the effects on the heart appear to be sufficient to explain all the observed effects on the circulation without postulation of any action on the peripheral vascular system.

Adrenergic blocking. Using the method of Hunt[3] no anti-adrenaline effect could be demonstrated.

Cholinergic blocking. *In vitro* experiments with intestine of rat, rabbit and monkey showed some atropine-like action in depressing methacholine-induced contractions. In these experiments it was shown to have about 1/500 to 1/1000 of the activity of atropine.

In vivo experiments in rats demonstrated that it could not inhibit the production of chromodacryorrhea induced by methacholine. Likewise no mydriatic effects could be demonstrated (mice).

SUMMARY

1. The diethylaminoethyl ester of benzylpenicillin is a substance of low toxicity when administered orally, subcutaneously or intramuscularly.

2. Intravenous administration may—according to the dose—cause either a transient drop in arterial blood pressure or complete circulatory failure due to cardiac arrest.

REFERENCES

1. Jensen *et al.*, *Acta Path. Microbiol. Scand.*, 1951, **28**, 407.
2. Juhl Nielsen *et al.*, to be published.
3. Hunt, *J. Pharmacol.*, 1949, **95**, 117.