

## Amelioration of the hypotensive effect of trypanocidal diamidines by use of heavy soluble salts

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**Abstract**—The influence of a heavy soluble dicaprylate salt preparation of a new trypanocidal diamidine (DiaPBF) on systolic and diastolic blood pressure and heart rate of rats has been compared with the effects of the easily soluble DiaPBF-dihydrochloride (DiaPBF-diHCl). After the dicaprylate the drop of the systolic blood pressure was 50% smaller than after an equimolar dosis of DiaPBF-diHCl.

For many years diamidines like pentamidine or diminazene have been used for the treatment of trypanosome infections in men and animals. The major hindrance for their widespread use is their broad spectrum of side effects, especially the depressive action on the cardiovascular system (Wien 1943; Steinmann et al 1986, 1987, 1988) resulting in a dangerous fall in blood pressure occurring immediately after parenteral application of the drugs. Therefore the heavy-soluble dicaprylate salt of the recently developed trypanocidal diamidine diamidinophenylbenzofuran (DiaPBF) was prepared in order to evaluate the possibility of reducing the sharp fall of the blood pressure by the use of sustained release of the compound.

### Material and methods

DiaPBF-diHCl (Fig. 1) was prepared as previously described (Dann et al 1971). The heavy-soluble DiaPBF-dicaprylate was

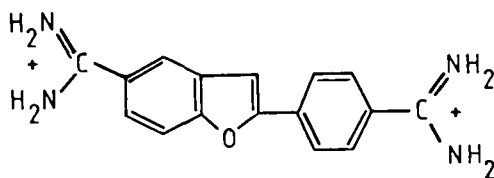


FIG. 1. DiaPBF

prepared by salting out from aqueous solution. For this purpose 10 mmol DiaPBF-diHCl and 2.2 mmol caprylic acid were dispersed in water. 0.1 M NaOH was added to pH 9.0. The quantitative precipitate was washed with icecold water and desiccated. For the injection the dicaprylate salt was redissolved and stabilized in a solution containing DiaPBF-dicaprylate 566 mg, Solutol HL 15 5.0 g, *N*-methylpyrrolidone 20.0 g and water 75.0 g.

**Measurement of the cardiovascular parameters.** The experiments were performed on male Wistar-rats. The experimental setup for the recording of the hemodynamic parameters (systolic and diastolic blood pressure, heart-rate) was as previously described (Steinmann et al 1986). 10  $\mu\text{mol kg}^{-1}$  DiaPBF-diHCl or DiaPBF-dicaprylate were injected i.v. through a catheter located in the femoral vein. The haemodynamic parameters were registered on-line on a Watanabe Mark V recorder. The results were analysed statistically by one way analysis of variance.

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### Results and discussion

At equimolar doses the dicaprylate salt caused a fall of the systolic blood pressure which was about 50% less than that produced by DiaPBF-diHCl. The effects on the diastolic blood pressure and on the heart rate were, however, the same with both preparations (Table 1). It seems, that both salts have similar

Table 1. Haemodynamic changes produced by DiaPBF-dihydrochloride and DiaPBF-dicaprylate.

Compounds	Arterial blood pressure		Heart-rate (beats $\text{min}^{-1}$ ) %
	Systolic (mm Hg) %	Diastolic (mm Hg) %	
DiaPBF			
—dihydrochloride	$-35.0 \pm 7.0$	$-49.0 \pm 7.8$	$+19.2 \pm 20.9$
—dicaprylate	$-17.8 \pm 2.6^*$	$-51.7 \pm 11.1$	$+24.3 \pm 17.3$

Peak effects; mean values  $\pm$  s.d.  
\* significant difference,  $P \leq 0.05$

effects on the vascular resistance but that the dicaprylate is less effective in reducing the cardiac performance. The results of this study indicate that the use of heavily soluble salts may, at least partially, prevent the immediate drop of the blood pressure after injection of diamidines. It is possible that the development of preparations that release the diamidines still more slowly, e.g. liposomes, may further enhance the safety of these compounds.

The authors thank Prof. Dr. O. Dann, Institute of Pharmacy, University of Erlangen-Nürnberg, for synthesis of DiaPBF-diHCl.

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