On the Metabolism of D-Penicillamine

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D-penicillamine, rat

D-Penicillamine (PA) is a potent drug in the treatment of hepatolenticular degeneration, rheumatoid arthritis, cystinuria and heavy metal poisoning. Much recent interest has centred on its pharmacokinetics. The question of whether PA, being excreted mainly with the urine [1–3], is subject to metabolic transformation and/or degradation, is still open. Milne [4] claims that approx. 50 per cent is degraded to anorganic sulphate. According to other authors [1, 5–7], however, the bulk of PA is excreted as PA-disulphide and as mixed disulphide with cysteine. These contradictory findings prompted us to determine the various urinary sulphur fractions following administration of PA. Some thiols, such as 2,3-dimercapto-propanol [8], are subject to glucuronidation. Therefore, we examined also whether this is true for PA.

Male rats of the Heiligenberg-strain with an average body weight of 150 g were injected intravenously with 10 mmoles PA/kg. This high dosage was not toxic and was chosen in order to get clear-cut results. The control animals received physiological saline. As the bulk of PA is excreted within few hours [1], the 6 hours-urine was collected. Sulphur was determined by the method of Kleeman *et al.* [9], glucuronic acid by the modified method of Maughan [10].

Table I. Excretion of sulphur compounds and glucuronic acid by rats after administration of D-penicillamine. Arithmetic means ± S.E. 6 rats per group.

	Amounts excreted [mg in 6 hours-urine] Control	PA
neutral sulphur	0.61 ± 0.22	17.15 ± 3.58
ethereal sulphur	0.26 ± 0.17	0.17 ± 0.074
free sulphate	2.56 ± 0.21	3.75 ± 0.65
glucuronic acid	15.04 ± 2.06	14.37 ± 1.50

As can be seen from Table I, there is neither an increase of the glucuronic acid nor of the ethereal sulphur. This may be taken as evidence that PA is not subject to glucuronic or sulphuric acid conjugation. The difference between the excreted amounts of anorganic sulphate does not reach statistical significance ($P = 0.12$). The lacking (or utmost marginal) degradation of PA to free sulphate is in agreement with an *in vitro*-study [11] showing that the SH-grouping of PA is not attacked by cysteine desulphhydrase. The increase in the neutral sulphur fraction, ascribable to the excretion of the PA-disulphides, amounts to 0.52 mmole, *i. e.* to 35 per cent of the administered PA-dose. This value is slightly lower than the excretion of ^{14}C-PA after injection of 0.1 mmole/kg [1]. However, one must take into acount that there is an inverse relationship between the excretion rate and dosage of PA [1].

From the metabolic point of view, PA is a virtually inert compound; this is easily explained by the fact that the extracellular water is the main dilution space of PA [12].

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[1] F. Planas-Bohne, Arzneimittel-Forsch. (Drug Res.) **22**, 1426 [1972].
[2] K. Gibbs and J. M. Walshe, Quart. J. Med. **XL**, 275 [1971].
[3] H. Schüßler, Arzneimittel-Forsch. (Drug Res.) **17**, 364 [1967].
[4] M. D. Milne, Annu. Rev. Pharmacol. **5**, 119 [1965].
[5] L. Eldjarn and L. Hambraeus, Scand. J. clin. Lab. Invest. **16**, 153 [1964].
[6] J. C. Crawhall and C. J. Thompson, Science [Washington] **147**, 1459 [1965].
[7] B. S. Hartley and J. M. Walshe, Lancet **II**, 434 [1963].
[8] G. H. Spray, Biochem. J. **41**, 366 [1947].
[9] C. R. Kleeman, E. Taborsky, and F. H. Epstein, Proc. Soc. exp. Biol. Med. **91**, 480 [1956].
[10] G. B. Maughan, K. A. Evelyn, and J. S. L. Browne, J. biol. Chemistry **126**, 567 [1938].
[11] H. V. Aposhian and L. S. Bradham, Biochem. Pharmacol. **3**, 38 [1959].
[12] E. Polig and F. Planas-Bohne, Biophysik in press.