Zusammenfassung

Die hemmende Wirkung wässeriger Leber- und Nierenextrakte von Mäusen auf die DOPA-Auto-Oxydation wurde geprüft. Leber- und Nierenwerte waren von gleicher Grössenordnung und etwa dreimal grösser als die früher für Mäuse- und Menschenhaut bestimmten Werte. Der Hemmfaktor besteht zum grossen Teil aus Eiweiss und konnte in einen -SH-Gruppen enthaltenden, hitzeempfindlichen Teil und einen -SH-Gruppen-freien, hitzestabilen Teil getrennt werden. Die mögliche Bedeutung solcher Hemmstoffe für die Zelle wird erörtert.

On the Elimination of Chlorprothixene in Rat and Man

Chlorprothixene[1], the trans isomer of 2-chloro-9-(3-dimethylaminopropylidene)-thiaxanthene, hydrochloride, is a new tranquillizing drug, the pharmacological properties of which have been reported previously[2,3] and which has been found to have promising clinical properties[4–7]. It is an analogue to chlorpromazine in which the phenothiazine ring system has been replaced by the thiaxanthene ring system to which the side chain is attached by a double bond. Like chlorpromazine it shows a fairly high ultraviolet absorbancy. UV maxima are obtained at 230, 268, and 325 mμ in aqueous solution. It is easily extracted from an alkaline aqueous solution into nonpolar solvents such as heptane or ether, and from these solvents into dilute acid. On addition of an equal volume of concentrated sulfuric acid to an aqueous solution, a weak salmon pink colour is obtained. The solution shows a main absorbance maximum at 389 mμ and additional maxima at 492 and 518 mμ. Furthermore, the solution shows intense yellow fluorescence (maximum at 559 mμ) on irradiation with UV light (around 3000–4000 Å). All these properties may be used for analysis qualitatively and quantitatively.

On analysis of urine from rats given the drug parenterally or orally, and from patients taking the drug orally, a sulfuric acid reaction as given above was found with extracts. The UV absorbance curves were not the same as obtained for the drug, however. Thus the presence of a metabolite was suspected and this was suggested to be the corresponding sulfoxide, in analogy to the case with a number of phenothiazine tranquillizers[8–11]. Synthetic chlorprothixene sulfoxide showed UV absorbance maxima at 221 and 261 mμ and a 'shoulder' at 310 mμ, and the UV absorbance curve was identical with the curves obtained for the urine extracts. On carrying out the sulfuric acid reaction, a salmon pink colour was obtained and the absorbance curve showed maxima at about 390 and 500 mμ; which is the same finding as for the urine extracts. No fluorescence in UV light was obtained for the synthetic sulfoxide or the urine extracts. On paper-chromatography in butanol-acetic acid-water, urine extracts gave a UV absorbing spot in the same position as the synthetic sulfoxide, R_f about 0·70, whereas the unchanged drug gave R_f about 0·75 and showed yellow fluorescence in long wave UV light after treatment with 50% sulfuric acid. No such reaction was obtained for the sulfoxide or the urine extracts.

After elution of the spot obtained with urine in dilute acid, a UV absorbance curve identical to that of the sulfoxide was obtained. On paper chromatography in 0·067 *M* phosphate buffer[12], pH 7·5, the sulfoxide and the urine extracts gave R_f about 0·70 and the drug R_f about 0·10. The identity of the urinary metabolite with the sulfoxide was thus concluded.

On quantitative analysis of the output of sulfoxide in urine (modified extraction according to SALZMAN and BRODIE[8] for separation of unchanged drug and sulfoxide; acetate buffer pH 5·4 was used), up to about 5% of the dose was recovered in 48 h on oral administration to rats (single dose, 25 mg/kg). In man 5·9–29·0%, with a mean of 11.7%, was recovered in 24 h (on continued administration with doses up to 100 mg thrice daily).

On analysis of feces (same method as for urine) unchanged drug as well as the sulfoxide was found, on oral administration in man. The total elimination in feces varied from 0–41% of the dose, somewhat more of the unchanged drug being eliminated. No other metabolites have been identified so far. In rats, only the sulfoxide metabolite was found in feces, and in amounts from 1–7% of the dose in 48–72 h on both oral and parenteral administration (single dose).

In the bile from bile-fistula-rats (light urethane-ether anesthesia), only sulfoxide was found and in amounts of the same order as in feces, after oral or intramuscular administration. After intravenous injection, however, up to 24% of the dose was recovered as sulfoxide from the bile within 7 h.

No detectable amounts of drug or sulfoxide were found in blood on oral administration to man, nor could the drug be determined in blood following oral or intramuscular administration of 25 mg/kg or intravenous injection of 5–10 mg/kg to rats. 2–5 min after intravenous injection of 25 mg/kg, a blood concentration in the order of 3–1 μg/ml was observed. The drug had disappeared from the blood in less than 10 min after injection.

L-G. ALLGÉN, B. JÖNSSON,
B. NAUCKHOFF*, M-L. ANDERSEN,
I. HUUS, and I. MØLLER NIELSEN**

Department of Clinical Chemistry and Department K II, Beckomberga Mental Hospital, Bromma (Sweden) and Research Laboratories of H. Lundbeck & Co. A/S, Copenhagen (Denmark)**, March 31, 1960.*

Zusammenfassung

Die Ausscheidung des neuen Neuroleptikums, Chlorprothixen, bei Menschen und Ratten wurde in Urin, Galle und Faeces untersucht und als einziges Abbauprodukt Chlorprothixen-Sulfoxyd gefunden. Ausscheidungsprodukte in % der verabreichten Dosis: Beim Menschen (orale Verabreichung) im Urin: 5–29% Sulfoxyd, Faeces: 0–41% unveränderter Stoff + Sulfoxyd. Bei der Ratte (orale oder parenterale Verabreichung) im Urin: bis zu 5% Sulfoxyd, Faeces: 1–7% Sulfoxyd, keine unveränderte Substanz, Galle: bis zu 24% Sulfoxyd.

[1] Truxal (N 714 trans, HCl), produced by H. Lundbeck & Co., Copenhagen (Denmark).

[2] P. V. PETERSEN, N. LASSEN, T. HOLM, R. KOPF, and I. MØLLER NIELSEN, Arzneim.-Forsch. *8*, 395 (1958).

[3] I. MØLLER NIELSEN and K. NEUHOLD, Acta pharmacol. toxicol. *15*, 335 (1959).

[4] E. MADSEN and J. RAVN, Nord. psykiat. Tidskr. *13*, 82 (1959).

[5] I. MØLLER NIELSEN, P. V. PETERSEN, and J. RAVN, Ugesk. læger *121*, 1433 (1959).

[6] M. ALSÉN and T. S:SON FREY, Sv. Läkartidn. *56*, 3344 (1959).

[7] O. H. ARNOLD, Wiener med. Wschr. *109*, 892 (1959).

[8] N. P. SALZMAN and B. B. BRODIE, J. Pharmacol. exp. Therap. *118*, 46 (1956).

[9] L-G. ALLGÉN, B. JÖNSSON, A. RAPPE, and R. DAHLBOM, Exper. *15*, 318 (1959).

[10] S. S. WALKENSTEIN and J. SEIFTER, J. Pharmacol. exp. Therap. *125*, 283 (1959).

[11] L-G. ALLGÉN, Paper read at the 7th Scand. Congr. on Clin. Chem. and Clin. Physiology, Helsingör (Denmark), 1959.

[12] T. BERTI and L. CIMA, Arch. int. Pharmacodyn. *98*, 452 (1954).