Acknowledgement—I would like to thank Wyeth Laboratories for providing the sodium γ-hydroxybutyrate used in this investigation.

New York State Research Institute for Neurochemistry and Drug Addiction, Ward's Island, New York, N.Y. 10035, U.S.A.

RENÉE K. MARGOLIS*

* Present address: Department of Pharmacology, Mount Sinai School of Medicine, New York, N.Y. 10029.

REFERENCES

1. H. LABORIT, *Int. J. Neuropharmac.* **3**, 433 (1964).
2. J. SOLWAY and M. S. SADOVE, *Anesth. and Analg.* **44**, 532 (1965).
3. D. R. METCALF, R. N. EMDE and J. T. STRIPE, *Electroenceph. clin. Neurophysiol.* **20**, 506 (1966).
4. R. H. ROTH and N. J. GIARMAN, *Biochem. Pharmac.* **15**, 1333 (1966).
5. M. WOLLEMANN and T. DEVENYI, *Agressologie* **4**, 593 (1963).
6. G. DELLA PIETRA, G. ILLIANO, V. CAPANO and R. RAVA, *Nature, Lond.* **210**, 733 (1966).
7. N. J. GIARMAN and K. F. SCHMIDT, *Br. J. Pharmac. Chemother.* **20**, 563 (1963).
8. C. MITOMA and S. E. NEUBAUER, *Experientia* **24**, 12 (1968).
9. R. H. ROTH and N. J. GIARMAN, *Biochem. Pharmac.* **18**, 247 (1969).
10. R. K. MARGOLIS, A. HELLER and R. Y. MOORE, *Brain Res.* **11**, 19 (1968).
11. S. A. BERL, A. LAJTHA and H. WAELSCH, *J. Neurochem.* **7**, 186 (1961).
12. N. OKUMURA, S. OTSUKI and H. NASU, *J. Biochem., Tokyo* **46**, 247 (1959).
13. G. H. MASSIEU, B. G. ORTEGA, A. SYRQUIN and M. TUENA, *J. Neurochem.* **9**, 143 (1962).
14. W. D. WINTERS and C. E. SPOONER, *Electroenceph. clin. Neurophysiol.* **18**, 287 (1965).
15. M. C. FLEMING and S. LACOURT, *Biochem. Pharmac.* **14**, 1905 (1965).
16. Y. GODIN and J. MARK, *C.r. Séanc. Soc. Biol.* **161**, 1392 (1967).
17. H. S. BACHELARD and J. R. LINDSAY, *Biochem. Pharmac.* **15**, 1053 (1966).
18. S. S. WALKENSTEIN, R. WISER, C. GUDMUNDSEN and H. KIMMEL, *Biochim. biophys. Acta* **86**, 640 (1964).
19. S. BERL, G. TAKAGAKI, D. D. CLARKE and H. WAELSCH, *J. biol. Chem.* **237**, 2562 (1962).
20. M. K. GAITONDE, D. R. DAHL and K. A. C. ELLIOTT, *Biochem. J.* **94**, 345 (1965).

Biochemical Pharmacology, Vol. 18, pp. 1246–1248. Pergamon Press. 1969. Printed in Great Britain

The effect of Metronidazol on the toxicity of ethanol

(*Received* 14 *October* 1968; *accepted* 4 *January* 1969)

METRONIDAZOL (hydroxy-2-ethyl,1-methyl-2-nitroimidazol) (M) was recently introduced in the treatment of alcoholism without offering experimental or clinical data, concerning its influence on the toxicity of ethanol (E).[1, 2, 5, 9–11]

The purpose of this paper is to present results concerning the acute and subacute toxicity of E in Metronidazol treated rats. Because Disulfiram (D) is also a drug widely used in the treatment of alcoholism, the experiments were carried out comparatively.

Materials and methods

Male rats, weighing 120–140 g, were used. The LD_{50} of a 50% E solution, administered by i.p.

route in groups pretreated with M or D at various intervals before or after the administration of E, was determined. The LD_{50} and safety limits were calculated by the probit method. M was administered i.p. and D, because of its lack of solubility, p.o. The 50 mg/kg M and 125 mg/kg D doses were chosen, being the minimum effective dose for the protraction of narcotic effect of E.[12]

The subacute toxicity of 2 doses of E was followed up in two experiments, in which E was followed up in two experiments, in which E was daily administered in a 33% solution. Some groups of rats were only given E, other groups E + M, or E + D. Groups treated with M or D alone were used concomitantly.

M synthesized in the Chemical and Pharmaceutical Research Institute and D (Antalcol)® were used

Results and discussions

Table 1 gives the results of the determination of the acute toxicity of E. It may be seen that in the animals which also got M, the toxicity of E was reduced, the most statistically significant results

TABLE 1. TOXICITY INDEX OF ETHANOL IN RATS (48 hr)

Substances	Dose (mg/kg)	Adm. route	Administration time	LD_{50} Safety limits (mg/kg)	No. animals
Ethanol (control)	—	—	—	3·6 (3·0–4·8)	110
Ethanol + Metronidazol	50	i.p.	concomitantly	6·0 (4·5–6·5)	40
Ethanol + Metronidazol	100	i.p.	24 + 1 hr before E	5·6 (4·9–6·5)	110
Ethanol + Metronidazol	50	i.p.	2 hr after E	4·9 (3·9–6·0)	30
Ethanol + Disulfiram	125	p.o.	1 hr before E	3·0 (2·0–4·2)	30

being found in the group treated with M 24 hr and 1 hr before the administration of E. However, the protective effect of M was also present in the groups treated concomitantly or even 2 hr after the administration of E. In the group treated with D the toxicity of E showed a slight increase.

Table 2 shows the mortality of the animals at the end of the subacute toxicity experiment. Among the M treated rats the mortality was lower than among the controls, and in the D treated rats higher

TABLE 2. ETHANOL SUBACUTE TOXICITY

Substances	Ethanol daily dose	Metronidazol daily dose	Disulfiram daily dose	Mortality abs.	No. days
Ethanol (control)	5 ml/kg	—	—	3/10	10
Eth. + Metron.	5 ml/kg	50 mg/kg i.p.	—	0/10	10
Eth. + Disulfiram	5 ml/kg	—	125 mg/kg p.o	8/10	10
Ethanol (control)	7 ml/kg	—	—	7/10	10
Eth. + Metron.	7 ml/kg	50 mg/kg i.p.	—	2/10	10
Eth. + Disulfiram	7 ml/kg	—	125 mg/kg p.o.	10/10	10
Metronidazol	—	50 mg/kg	—	0/10	10
Disulfiram	—	—	125 mg/kg p.o.	0/10	10

The experimental results proved the protective action of M, in contrast to D, against acute and subacute E toxicities. In other experiments, it was observed that a single administration of E after pretreatment with either M or D was followed by a prolonged narcosis[12] which can be explained by the inhibition of alcohol-dehydrogenase and other alcohol oxidizing enzymes, an effect already described for D and M *in vitro*.[3, 4, 8] The protective effect of M against E acute and subacute toxicities appears to be independent of the intensity of the central (narcotic) effect of E, due to the possibility of protection present also 2 hr after E administration, at a time when the narcotic effect is over.

The intimate mechanism of this protection is not yet known but it might be assumed that M

reduces the cellular necrosis provoked by E. Preliminary experiments show that M also exerts a hepatoprotective effect with respect to fatty loading of the liver induced by E, reducing the high lipid content and preventing the onset of histologic fatty degeneration lesions. Bearing in mind that M inhibits the release of adrenal hormones,[7] incriminated in the toxic action of E and in lipid mobilisation,[11] it is not excluded that its effect would occur also at this level.

In conclusion, the experimental data sustain the advantage of using M in the treatment of alcoholism in comparison with D, thus suppressing not only the need for alcohol drinking but also exerting an antitoxic action with regard to the acute and subacute E toxicity.

The Chemical and Pharmaceutical Research Institute,
Bucarest,
Sos. Vitan Nr.112, R.S. Romania

D. WINTER
C. STĂNESCU
S. SAUVARD
I. NIȚELEA

REFERENCES

1. A. BLOM, *Lakartidingen* suppl. 1 57 (1967).
2. B. CAMPBELL, J. TAYLOR and W. HASLETT, *Proc. Soc. Exp. Biol. Med.* **124**, 1911 (1967).
3. J. A. EDWARDS, J. PRICE, *Biochem. Pharmac.* **16**, 2026 (1967).
4. R. FRIED and L. W. FRIED, *Biochem. Pharmac.* **15**, 1890 (1966).
5. B. LAMPO, *Minerva Med.* **58**, 2531 (1967).
6. H. E. LEHMAN, T. A. BAN and E. NATACHAYAN, *Psychiat. Neurol.* **152**, 395 (1966).
7. T. MAHLIN, B. ASTEDT and L. KVINOKLIN, *Nord. Med.* **74**, 1072 (1965).
8. E. PALTRINIERI, *Il Farmaco (Sci.)* **22**, 1054 (1967).
9. M. SEMER, PH. FRIEDLAND, M. VAISBERG and A. GREENBERG, *Am. J. Psych.* **123**, 722 (1966).
10. G. SOGLIANI and B. MILANI, *Minerva Med.* **58**, 1510 (1967).
11. J. TRÉMOLIÈRES and R. LOWY, *Actualité Pharm.* 191 (1964).
12. D. WINTER, S. SAUVARD, C. STĂNESCU, M. THEODORESCU, J. WINTER and I. NITELEA, *Med. Pharm. Ex.* (in press).

Biochemical Pharmacology, Vol. 18, pp. 1248–1251. Pergamon Press. 1969. Printed in Great Britain

The influence of psychotropic drugs and ambient temperature on glycogen and reducing substances in mouse brain and liver*

(*Received* 11 *November* 1968; *accepted* 8 *January* 1969)

CHLORPROMAZINE alters the pattern of glucose metabolism in mouse brain *in vivo*. Following administration of the drug, a single dose of ^{14}C glucose is more slowly converted to lipids and protein and there is a higher proportion of radioactive counts in the acid soluble extract of the brain homogenate which contains amino acids and sugars.[1] Using a glucose oxidase method chlorpromazine has been shown to increase the acid hydrolysable fraction of mouse brain carbohydrate, i.e. glycogen and/or glucose phosphates.[2] A possible cause of these changes is the fall in body temperature produced by chlorpromazine.[3] In this experiment the ambient temperature of mice was maintained between 31° and 33° and the effects of administration of chlorpromazine, imipramine and pentobarbitone on brain reducing substances and glycogen were measured.

Adult albino mice (SAS/ICI) of either sex weighing 36–48 g were used. Ambient temperatures were controlled by placing perspex mouse boxes in a L.T.B. incubator. Each mouse box contained

* This work was supported by a United Cerebral Palsy Grant.