

Dimethylformamide and alcohol intolerance

W. H. LYLE*, T. W. M. SPENCE, W. M. MCKINNELEY, AND K. DUCKERS

From Dista Products Limited, Fleming Road, Speke, Liverpool

ABSTRACT Facial flushing and other symptoms were reported by 19 of a group of 102 men who worked with dimethylformamide (DMF). Twenty-six of the 34 episodes occurred after the workers had consumed alcoholic drinks. The metabolite N-methylformamide (MF) was detected in the urine on 45 occasions, the highest recorded concentration being 77 $\mu\text{l/litre}$. The highest recorded concentration of DMF in air was 200 ppm. The DMF-ethanol reaction is possibly attributable to the inhibition of acetaldehyde metabolism, probably by MF.

Most of the symptoms of the disulfiram-ethanol interaction are considered to result from the accumulation of acetaldehyde following the blocking of aldehyde dehydrogenase. Specifically, flushing of the skin can be induced by the injection of acetaldehyde (Sauter *et al.*, 1977).

Alcoholic beverages drunk after exposure to dimethylformamide (DMF) are known to induce symptoms rather like those induced by the combination of disulfiram or cyanamide with ethanol (Tolot *et al.*, 1958; Reinl and Urban, 1965). Hanasono and his colleagues (1977) showed that DMF or disulfiram administered (each in doses of 2 mmol/kg) to rats increased the blood acetaldehyde levels of these animals four- and five-fold respectively in response to ethanol (2 g/kg) given 18, but not three, hours later. An equivalent dose of N-methylformamide (MF) raised blood acetaldehyde levels equally, whether given three or 18 h before ethanol challenge.

Eben and Kimmerle (1976) have shown that, in volunteers exposed for two hours to an atmosphere containing 50-80 ppm of DMF, blood DMF concentrations were of the order of 9.9 $\mu\text{g/ml}$ and had fallen to undetectable levels within six hours. Blood MF over the same period rose from a mean of 2.5 $\mu\text{g/ml}$ to 3.2 $\mu\text{g/ml}$ and was still detectable in traces after 30 h.

One hundred and two men, at various times over a period of three years, were engaged in running a chemical plant in which DMF was used as a solvent. Shortly after operations began in early 1974 some of the men reported that their customary

evening beer caused unusual flushing, mainly of the face and exposed parts, and sometimes dizziness, nausea and tightness of the chest. In the light of the interaction between DMF and ethanol a register was kept to record symptoms attributed to DMF, and relevant biochemical and environmental tests were carried out.

Methods

WORK PLACE AND WORK PATTERN

The plant comprised standard reaction vessels, centrifuges and fluidised bed driers, with appropriate localised ventilation, and was contained in a single building. Exposure to DMF might occur during transfer of the solvent from store to reaction vessels, and during filtration and drying of the final product. The completion of one batch took approximately 48 h and successive batches were produced continuously by teams of 10 men working in five shifts.

AIR TESTING

DMF in air was estimated from March 1974 until August 1975 by Draeger tube at the same four points in the plant once daily, with additional readings when leakage was suspected. During this period, therefore, there were at least four tests each day. After August 1975 the frequency of testing was drastically reduced because only rarely were concentrations of 10 ppm or more being recorded.

REGISTER OF SYMPTOMS

The Register was a ledger in which were recorded the subject's name and rota number, with a description of his symptoms, when and where these were experienced, when recorded, the date of the last shift, any history of other episodes, details of the specific

*Correspondence to W. H. Lyle: present address Courtauld's Ltd, 18 Hanover Square, London W1.

Received for publication 10 April 1978

Accepted for publication 7 September 1978

job, and any other factors. The Register was kept at the plant and was filled in by the subject concerned. It was started in March 1974 and remained available for entries throughout the three-year period of the study.

URINE TESTING

Frequency of sampling

From the beginning of January 1976 until the end of the year, specimens of urine were collected each week from five of the 10 men working on the last morning shift; as a result of the shift system in operation, therefore, each man on the plant had his urine examined once every 10 weeks.

Chemical methods

MF in urine was determined by gas chromatography according to the method of Barnes and Henry (1974). The lower limit of detection was 10 $\mu\text{l/l}$.

Analysis of δ -aminolevulinic acid (ALA) and porphobilinogen (PBG) was carried out colorimetrically with Ehrlich's reagent on one set of 25 urine samples, by a modification (Davis and Andelmann, 1967) of the method of Mauzerall and Granick (1956).

Results

RELATIONSHIP OF DMF IN AIR TO REPORTS OF FLUSHING

Twenty-eight of the 32 recorded occasions on which DMF in air exceeded 20 ppm in the working atmosphere, and 22 of the 34 reports of flushing, occurred during the first three months of this study. The relationship between DMF in air and reports of flushing during 1974 and 1975, when Draeger testing was routinely performed daily, are summarised in the Table. The three highest recorded

Table 1 *Frequency of flushing and of ambient DMF concentration exceeding 10 ppm, with maximum recorded*

Date	Number of cases of flushing reported	DMF in air	
		> 10 ppm (n)	Maximum recorded (ppm)
1974			
1 March-31 May	22	79	200
1 June-31 Dec.	5	16	150
1975			
1 Jan.-31 Dec.	5	24	35

concentrations of DMF in air throughout the period were, on one occasion each, 200, 150 and 60 ppm; none of these coincided with reports of flushing.

RELATIONSHIP OF MF IN URINE TO REPORTS OF FLUSHING

Urine testing began at a time when reports of over 10 ppm DMF in air had become rare events. Of 333 assays of MF in urine during 1976, 288 yielded results below 10 $\mu\text{l/l}$. Fifteen exceeded 20 $\mu\text{l/l}$, and the three highest were 54, 62 and 77 $\mu\text{l/l}$, each on one occasion, and did not coincide with any of the four reports of flushing recorded during the year, nor with a report of raised DMF in air.

All specimens of urine were negative for PBG. ALA concentrations were within the normal range.

SYMPTOMS AND RELATIONSHIP TO ALCOHOL INTAKE

Of the 102 men who had worked in the plant at some time during the period of observation, 29 made a total of 57 entries in the Register, soon known to all as the 'Flush Book'. Nineteen subjects recorded 34 episodes of flushing that always affected the face and often the neck, hands, arms, and chest. Eleven of these subjects reported that they had previously experienced, but had not recorded, the same phenomenon on other occasions. Twenty-six of the recorded episodes had occurred after imbibing alcoholic drinks, usually at a public house. The other episodes may, in fact, also have been precipitated by alcohol, but this information was not volunteered and had not specifically been sought, in order to avoid suggestion.

Flushing, always very conspicuous, was not accompanied by sweating though often by a sense of warmth, but was associated in three subjects with dizziness. Palpitation, nausea, breathlessness and transient loss of consciousness (in the last case late on Christmas Eve) occurred with flushing, each in one individual.

The remaining 23 reports were of various combinations of dizziness, coryza, cough, rash and tightness of the chest, not usually repeated in any one subject, and associated neither with flushing nor, apparently, with the consumption of alcohol.

The majority of those who had worked in the plant failed to record any symptoms in the Register, although there was hearsay evidence that some of these had been seen to be affected while drinking at a public house in the company of others who had recorded their own symptoms. We cannot be sure that DMF-induced flushing occurred only in response to alcohol challenge.

Severe abdominal pain after exposure to DMF, reported by Potter (1973) and Chary (1974), was not recorded by any of our subjects.

DURATION OF EFFECT

Under the shift system in operation, men were in

turn absent from the plant for periods of two, three and four days. Alcoholic drinks taken as late as the fourth day after the last shift worked were said to have caused vivid flushing, although the majority of reports indicate that the reaction occurred within 24 h of exposure to DMF. A single glass of beer was sufficient to induce a flush that lasted from one to two hours and did not recur even if further liquor was taken.

Discussion

The prevalence of mild symptoms of apparent DMF-ethanol interaction was greater among our subjects than had been expected from the sparse references in the literature, possibly because facial flushing on drinking alcohol is a source of hilarity rather than alarm. However, more serious reactions to DMF suggestive of acute pancreatitis (Chary, 1974), peptic ulcer, biliary tract disease or acute intermittent porphyria (Potter, 1973) have been reported, although it is not clear whether these were precipitated by ethanol. The absence from our group of any such reaction is probably because exposure to DMF was less. Thus, we did not detect PBG in urine collected at a time when DMF in air was usually less than 10 ppm and urine MF less than 10 $\mu\text{l/l}$.

Krivanek *et al.* (1978), using the same method of assay of MF in urine (Barnes and Henry, 1974), have shown that volunteers exposed to concentrations of DMF in air of approximately 10 ppm for six hours daily for five days excreted MF in their urine at a peak rate of about 0.25 $\mu\text{l/h}$, within three hours of the cessation of exposure each day. The mean MF concentration in urine collected in the first seven hours after exposure was 4.7 $\mu\text{l/l}$, and in 24 hours' urine, 0.73 $\mu\text{l/l}$. There was no significant difference in MF excretion from day to day. As in at least 15 cases we obtained significantly higher urinary MF excretion than the peak MF excretion after exposure to 10 ppm, it seems highly likely that exposure to DMF in air was at that time above 10 ppm.

Reports of flushing were most numerous before urine testing for MF had begun and we cannot, therefore, correlate the two. From their own observations and those of Eben and Kimmerle (1976), Krivanek *et al.* (1978) showed that there is a linear relationship between 24 h MF excretion and DMF exposure, so that there can be no doubt that at the time when flushing was prevalent and DMF in air was sometimes present in greater concentrations than those used experimentally by Eben and Kimmerle, our subjects must have been excreting substantial amounts of MF for many hours after exposure. Eben and Kimmerle, who had exposed volunteers to 53 ± 32 ppm of DMF for two hours, failed to detect

DMF in urine after eight hours, though traces of MF were present up to 48 h after exposure.

The flushing and occasional dizziness that so promptly followed ingestion of quite small amounts of beer by our subjects many hours after exposure to DMF, as in the patient reported by Chivers (1978), occur also as part of the disulfiram-ethanol reaction. Anxiety, blurred vision, cardiac collapse or convulsions, which constitute the more severe manifestations of disulfiram-induced sensitivity to ethanol, did not affect our subjects. This might have been because the dose of DMF was too small to induce such effects, or because disulfiram has a wider range of action than DMF. Undoubtedly the administration of disulfiram and of DMF leads to the accumulation of acetaldehyde in the blood, and the injection of acetaldehyde alone induces flushing, hyperventilation and tachycardia (Sauter *et al.*, 1977). All the effects of the DMF-alcohol interaction in our subjects might reasonably be attributed to acetaldehyde.

The demonstration by Eben and Kimmerle (1976) that DMF is rapidly cleared from the blood while MF persists for long periods, together with the observation of Hanasono *et al.* (1977) that ethanol challenge raises blood acetaldehyde levels much more rapidly after MF than after DMF, indicate that the metabolite, MF, is the active agent in the inhibition of acetaldehyde metabolism in man. Eben and Kimmerle (1976) give indirect support to this interpretation by their experiment in which volunteers took 19 g ethanol *before* being exposed for two hours to an atmosphere containing 80 ppm of DMF. The subjects did not develop any symptoms, and there was no increase in blood acetaldehyde. The rate of DMF demethylation was reduced.

If the DMF-ethanol reaction is an example of a pharmacological reaction mediated by a metabolite and is dependent upon the rate of demethylation of a given dose of DMF, this may explain some of the observed individual variations in response.

Monitoring of MF in urine is a rational and useful means of control of DMF exposure. Those who work with DMF should be warned of possible alcohol sensitisation and urged to report relevant symptoms.

We are obliged to Dr D. Malcolm and to Du Pont and Co for advice on urine testing for MF.

References

- Barnes, J. R., and Henry, N. W. (1974). The determination of N-methylformamide and N-methylacetamide in urine. *American Industrial Hygiene Association Journal*, **35**, 84-87.

- Chary, S. (1974). Dimethylformamide: a cause of pancreatitis. *Lancet*, **2**, 356.
- Chivers, C. P. (1978). Disulfiram effect from inhalation of dimethylformamide. *Lancet*, **1**, 331.
- Davis, J. R., and Andelmann, S. L. (1967). Urinary delta-aminolaevulinic acid (ALA) levels in lead poisoning. *Archives of Environmental Health*, **15**, 53-59.
- Eben, A., and Kimmerle, G. (1976). Metabolism studies of N, N-dimethylformamide. III. Studies of the influence of ethanol in persons and laboratory animals. *International Archives of Occupational and Environmental Health*, **36**, 243-265.
- Hanasono, G. K., Fuller, R. W., Broddle, W. D., and Gibson, W. R. (1977). Studies on the effects of N, N-dimethylformamide on ethanol disposition and monoamine oxidase activity in rats. *Toxicology and Applied Pharmacology*, **39**, 461-472.
- Krivanek, N. D., McLaughlin, M., and Fayerweather, W. E. (1978). Monomethylformamide levels in human urine after repetitive exposure to dimethylformamide vapour. *Journal of Occupational Medicine*, **20**, 179-182.
- Mauzerall, D., and Granick, S. (1956). The occurrence and determination of acid and porphobilinogen in urine. *Journal of Biological Chemistry*, **219**, 435-446.
- Potter, H. P. (1973). Dimethylformamide-induced abdominal pain and liver injury. *Archives of Environmental Health*, **27**, 340-341.
- Reinl, W., and Urban, H. J. (1965). Erkrankungen durch Dimethylformamid. *Internationales Archiv für Gewerbe-pathologie und Gewerbehygiene*, **21**, 333-346.
- Sauter, A. M., Boss, D., and von Warburg, J. P. (1977). Revaluation of the disulfiram-alcohol reaction in man. *Journal of Studies on Alcohol*, **38**, 1680-1695.
- Tolot, F., Droin, M., and Genevois, M. (1958). Intoxication par la dimethylformamide. *Archives des Maladies Professionnelles de Medicine du Travail et de Sécurité Sociale*, **19**, 602-606.