

Correspondence

Cadmium, NAG activity, and β_2 -microglobulin in the urine of cadmium pigment workers

SIR,—Our attention has been drawn by the recent paper of Kawada *et al* (1989;46:52–5) recommending the assay of urinary β -N-acetylglucosaminidase (NAG) as “a more sensitive indicator of cadmium (Cd) absorption than β_2 -microglobulin” (BMG). This recommendation relies on the observation that NAG correlates more closely with Cd in urine concentrations than urinary BMG in workers excreting less than 10 g Cd/g creatinine.

To assess the usefulness of urinary NAG as a marker of Cd nephrotoxicity, however, at least two questions must be considered. The first is whether an increased urinary excretion of NAG is more prevalent than that of BMG after chronic exposure to Cd. The data provided by Kawada *et al* do not permit a direct comparison between the prevalences of abnormal values of both markers. We could nevertheless estimate the upper limit of normal for the urinary excretion of NAG and BMG by calculating the geometric mean +2 geometric SD from the data presented in table 2. The cut off levels for NAG and BMG were estimated at about 4.8 U/g cr and 195 μ g/g cr respectively. It is evident from fig 1 that most values of urinary NAG are in the normal range. Only about four or five values (from a total of 61) are higher than the cut off level but this number of abnormal NAG results is certainly lower than that for BMG as judged from table 1.

The second important question concerns the biological significance of the raised NAG excretion induced by Cd. With respect to BMG, it is now well established that, in the absence of a lowered glomerular filtration rate, a raised urinary excretion reflects a proximal tubular defect that may be the starting point of a progressive loss of renal parenchyma if exposure to Cd is maintained.¹ The interpretation of raised urinary NAG is less straightforward owing to the different mechanisms that may cause an increased NAG excretion. In man and in rats the activity of NAG in urine originates almost exclusively from the renal enzyme actively secreted in urine by exocytosis.² This functional enzymuria is linked to the A isoenzyme of NAG, which is part of the soluble intralysosomal compartment.³ The NAG excretion may also be increased by damage to the tubular cell or the lysosomes. This lesional enzymuria is characterised by the excretion of the B isoenzyme of NAG linked to the lysosomal membrane.

At the early stage of exposure to Cd, the increased NAG activity in urine could conceivably result from a

British Journal of Industrial Medicine 1989;46:679–680

stimulation by the metal of exocytosis or of the NAG activity in the kidney, or both, as observed with aminoglycosides.^{4,5} Under these conditions, urinary NAG would be more a reflection of the renal store of Cd than of proximal tubular damage. At a more advanced stage, a lysosomal enzymuria may appear as a consequence of proximal tubular damage. As documented by human or animal studies, however, owing to the relatively high background of NAG in urine, NAG is a less sensitive index of tubular injury than low molecular weight proteins which are nearly completely reabsorbed by the proximal tubule.^{6,7}

In the absence of information on the isoenzyme profile the slight increases of NAG excretion observed at the early stage of exposure to Cd must be interpreted with caution since, by contrast with low molecular weight problems, NAG is a secretory product of the kidney that does not constitute an unequivocal marker of nephrotoxicity.

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References

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Drs Kawada, Koyama, and Suzuki reply:

The first question raised by Bernard and Lauwerys is not valid because the higher prevalence of abnormal BMG results compared with NAG does not suggest

that BMG is a more important biomedical indicator of exposure to cadmium. As shown in tables 2 and 3, BMG shows little dose response relation with Cd in the urine with exposure, whereas NAG does. Moreover, the variance of BMG in the exposed group is greater than that of the non-exposed group, and the mean BMG value of the exposed group is lower than in the other groups studied. These observations limit the usefulness of BMG as an indicator of the effects of low level exposure to Cd.

Regarding the second question, we did not measure the isoenzyme of NAG and we are aware that different biological mechanisms have been proposed for the excretion of NAG A and B in the urine.¹⁻³ In our paper, however, we have emphasised the importance of NAG as an indicator of the cumulative effect of cadmium before there is an increase in BMG reflecting proximal tubular dysfunction. NAG measurements are recommended as the earliest indicator of the accumulation in the kidney; we do not propose it as an indicator of malabsorption by the renal proximal tubular cell.

Studies by Lauwerys and his coworkers have shown a significant relation between urinary BMG and Cd in the urine above a mean value of 10 µg Cd/g creatinine.^{4,5} We agree (above this level) that BMG is a good indicator of renal proximal tubular damage caused by absorption and accumulation of Cd. The effects of low level exposure of workers to chemical substances, however, should be detected at the earliest possible time. Other workers have also concluded that the excretion of NAG in the urine might precede that of BMG, possibly due to earlier effects on the renal tubular cells.^{6,7} Recently, we have carried out another study in the same factory and obtained further data

which support the conclusions in our paper.⁸ Correlation coefficients between the logarithm of Cd in the urine and of NAG and BMG were 0.45 and 0.05, respectively. We also assessed urinary metallothionein (MT-U) and blood cadmium concentrations. MT-U is a useful indicator of absorption and accumulation of Cd but not of the biomedical effect.

References

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Notice

International Workshop on Pharmacokinetic Modelling in Occupational Health, Leysin, Switzerland, 5-7 March 1990

Pharmacokinetic models are used to solve occupational health problems by more and more research groups. The goal of this workshop, organised jointly by the Institute of Occupational Health Sciences (Lausanne, Switzerland) and the National Institute of Occupational Health (Solna, Sweden), and

sponsored by the European Society of Toxicology, is to bring together modellers to exchange experiences and ideas. Invited speakers will explore various uses of models in topics such as biological monitoring, epidemiology, species extrapolation, risk assessment, and biological variability. For details, contact Dr P O Droz, Institute of Occupational Health Science, Avenue du Bugnon 19, 1005 Lausanne, Switzerland, before 30 September 1989.