CASE REPORT

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A Death Involving Probenecid

REFERENCE: McIntyre, I. M., Crump, K., Roberts, A. N., and Drummer, O. H., "**A Death Involving Probenecid,**" *Journal of Forensic Sciences*, JFSCA, Vol. 37, No. 4, July 1992, pp. 1190–1193.

ABSTRACT: A death following deliberate ingestion of approximately 75 g of probenecid in a 36-year-old man is described. Tissue concentrations of probenecid were highest in serum (710 mg/L) and liver (550 mg/kg). Probenecid was also detected in vitreous and bile. Ethanol was also detected in blood at 0.13 g/100 mL.

KEYWORDS: toxicology, probenecid, poisoning, ethanol

Probenecid [4-(dipropylsulfamoyl) benzoic acid] is a uricosuric agent used in the treatment of chronic gout. It may also be used to enhance plasma concentrations of penicillin, antibiotics, non-steroidal anti-inflammatory drugs [*1*] and captopril [*2*] by reducing tubular secretion.

Fatal poisoning by probenecid is not known. We report here the death of a man following a deliberate overdosage with probenecid, accompanied by alcohol ingestion. The post mortem alcohol concentration in itself was considered unlikely to be lethal.

Case History

The deceased was an obese, 36-year-old male who had a long history of alcohol abuse and was known to be depressed following the breakup of his marriage. He had made an unsuccessful attempt at suicide some 18 months prior to his death, which had resulted in an acute psychiatric referral and a diagnosis of alcohol-related aggression, but no long-term treatment or follow-up eventuated.

The deceased was found semi-conscious seated on a toilet. He was incoherent and was noted to be perspiring profusely and to have vomited and excreted all over the floor. It was reported that the deceased had consumed alcohol and approximately 150 (500 mg) probenecid (Benemid) tablets that had been prescribed to the deceased for gout. Earlier that day, he had attempted to stab himself in the chest whilst under the influence of alcohol.

He was transported to the hospital in a conscious state, but rapidly deteriorated, lapsing into coma and suffering several epileptiform seizures. Plans were made to transport him

Received for publication 1 Nov. 1991; revised manuscript received 14 Dec. 1991; accepted for publication 16 Dec. 1991.

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to a larger medical center, but his blood pressure fell, he suffered a cardiac arrest and died some 4 h after presentation.

Methods and Materials

Instrumentation

The liquid chromatograph consisted of two Model 6AD pumps, a gradient mixing chamber, Model SIL-6B autoinjector, system controller (SCL-6B), Model SPD-M6A photodiode array detector (Shimadzu Instruments) and a PC-AD computer (Samsung S550). A back-up drive, an additional Model SPD 6AV ultraviolet detector operating at 230 nm and a Model CR-4A integrator/plotter (Shimadzu Instruments) was connected in series with the photodiode array detector. The photodiode array detector was operated in 1 nm band-pass mode. Display wavelengths were 230 nm and 214 nm. A spherisorb 5S-ODS-2 (15 cm by 3.8 mm I.D.) column was used protected by a NOVAPAK C18 guard column (Waters Associates).

Chromatography

For specimen screening, a gradient system was used. Mobile phases consisted of 10% acetonitrile in 10 mM potassium phosphate buffer pH 3.1 (Pump A) and 60% acetonitrile in 10 mM potassium phosphate buffer, pH 3.1 (Pump B). Gradient conditions used were: isocratic at 0% B for 1 min, linear gradient to 50% Pump B over 5 min, isocratic at 50% Pump B for 20 min then a linear gradient to 100% Pump B over 10 min followed by a hold at 100% Pump B for 5 min. Total flow rate was 1.0 mL/min. At the completion of the run the pumps were programmed to 0% B over 5 min. A 15 min reconditioning time was used between runs.

Quantification of probenecid was performed using isocratic conditions. The mobile phase was methanol/acetonitrile/15 mM potassium phosphate buffer (43:14:43), pH 4.0 at a flow rate of 0.8 mL/min. Detection wavelength was 214 nm. All other chromatographic conditions were identical to the screening procedure. The retention times for probenecid and internal standard were 3.8 and 6.1 min, respectively.

Experimental Procedures

Post mortem blood, serum, urine, bile, vitreous, liver homogenate, and gastric contents were analyzed for probenecid. Extraction of probenecid was achieved by adding 0.25 mL of acetonitrile containing internal standard (80 mg/L of 5-(4-methyl phenyl)-5-phenyl-hydantoin) to an equal volume of postmortem fluid or liver homogenate. Standards were prepared in drug-free pooled tissues containing (blank), 50, 100, 200, and 500 mg/L of probenecid. Liver homogenates were prepared by homogenizing 10 g liver with 10 mL of water, adjusting pH to 10 and digesting with 10 mg of subtilisin for 2 h at 60°C. The pH was brought back to 7.0 before further use.

Samples were injected (10 μL) using the isocratic chromatographic conditions described, and peak height ratios of probenecid to internal standard calculated. The concentration of probenecid was calculated from the calibration curve.

Probenecid was confirmed by match of UV spectra to an authentic standard and similarity of relative retention time to internal standard.

Blood was measured for ethanol using gas chromatography. Urine and bile was subjected to a drug screen for propoxyphene, barbiturates, benzodiazepines, and for illicit drugs including amphetamines, cocaine and opiates. Blood was also subjected to a comprehensive drug screen using capillary gas chromatography with nitrogen phosphorous

TABLE 1—*Post mortem concentration of drugs in a death involving probenecid.*

Probenecid	- serum	710 mg/L
	- liver	550 mg/kg
	- blood	460 mg/L
	- bile	340 mg/L
	- urine	240 mg/L
	- vitreous humour	180 mg/L
	- gastric contents	11 mg
Ethanol	- blood	0.13 g/100 mL
	- urine	0.16 g/100 mL

detection of a butyl chloride basic extract. This technique is able to detect anti-depressant, anti-psychotic, benzodiazepine, narcotic, and other drugs.

Results and Discussion

Post-mortem examination of this obese man revealed an enlarged heart due to moderate left ventricular hypertrophy. However, valves and cusps were healthy. There was no evidence of systemic hypertension, atheroma, or ischemic changes in the myocardium. The lungs were heavy and congested with mild edema. Airways were clear, but a mild excess of clear mucus was present. The brain was congested and the liver was fatty. These and other organs were otherwise unremarkable. There were multiple fine linear scars over the anterior abdomen, which were consistent with a recent self-inflicted origin.

Probenecid was detected in all specimens tested, the highest concentrations found in serum and liver (Table 1). High concentrations were also detected in bile and vitreous humour. Because the time from ingestion to death was not less than 4 h, it was interesting to note that 11 mg of probenecid remained in the gastric contents. The usual therapeutic dose of probenecid is up to 2 g daily. Consequently, the presumed dose of 75 g used in this fatal poisoning is well in excess of that used therapeutically.

Plasma concentrations of probenecid following an oral dose of 2 g have been shown to peak at 149 mg/L at between 3 to 4 h [*3*]. This is significantly less than the serum concentration of probenecid of 710 mg/L detected in the deceased.

The presence of probenecid in significant concentrations in bile demonstrates for the first time that probenecid is excreted into bile in humans [*1*]. The blood/serum ratio and the lower liver concentration to serum is consistent with the reported low volume of distribution of probenecid [*1*].

The coroner returned the finding that the deceased took his own life from an overdose of drugs and that no other person contributed to the death.

Acknowledgment

We thank the coroner for making his files available. We also wish to thank Ceril Pereira for typing the manuscript.

References

[*1*] Cunningham, R. F., Israilis, Z. H., and Dayton, P. G., "Clinical Pharmacokinetics of Probenecid," *Clinical Pharmacokinetics*, Vol. 6, 1981, pp. 135–151.

[*2*] Drummer, O. H., Thompson, J., Hooper, R., and Jarrott, B., "Effect of Probenecid on the Disposition of Captopril and Captopril Dimer in the Rat," *Biochemical Pharmacology*, Vol. 34, 1985, pp. 3347–3351.

[3] Selen, A., Amidon, G. L., and Welling, P. G., "Pharmacokinetics of Probenecid Following Oral Doses to Human Volunteers," *Journal of Pharmaceutical Science*, Vol. 71, 1982, pp. 1238–1242.

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