frusemide (Wilson *et al.*, 1975) and bumetanide (Hunter & Underwood, 1975). A suggested explanation for the augmented effect of twice daily administration is that the second dose of diuretic interrupts a period of relative sodium retention mediated via the renin-aldosterone system as a homeostatic response to the first diuresis. If this mechanism is relevant, it may be that piretanide, which achieves a total diuretic effect comparable to frusemide by a slightly more gradual and prolonged duration of action, induces a less vigorous antinatriuresis and so does not achieve a comparably enhanced effect when administered twice daily. Alternatively it may be explained on the basis of the pharmacokinetic observation that incremental administration of a drug results in a significantly greater area under the response-time curve, as compared to a single total dose (Wagner, 1968).

References

- BRITISH MEDICAL JOURNAL (1979). Management of refractory oedema. *Br. med. J.*, **i**, 148-149.
- HUNTER, K.R. & UNDERWOOD, P.M. (1975). Evaluation of once-daily versus twice-daily bumetanide in heart failure. *Postgrad. med. J.*, **51** (Suppl. 6), 91-95.
- ROBERTS, C.J.C., HOMEIDA, M., ROBERTS, F. & BOGIE, W. (1978). Effects of piretanide, bumetanide and frusemide on electrolyte and urate excretion in normal subjects. *Br. J. clin. Pharmac.*, **6**, 129-133.
- WAGNER, J.G. (1968). Kinetics of pharmacologic response. *J. theor. Biol.*, **20**, 173-201.
- WILSON, T.W., FALK, K.J., LABELLE, J.L. & NGUYEN, K.B. (1975). Effects of dosage regimen on natriuretic response to furosemide. *Clin. Pharmac. Ther.*, **18**, 165-169.

Whatever the importance of these suggested mechanisms, they are compatible with our finding that diuresis and natriuresis are at least as great with a half-dosage, twice-daily regimen. Diuretic effect is probably governed by the total daily dosage of loop diuretic (and the total amount reaching the tubular lumen) and is not significantly influenced by different schedules of dose administration. In practice this means that the dosage schedule may be tailored to suit the individual patient's requirements without impairment of overall diuretic effect.

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RENAL CONVERSION OF PLASMA DOPA TO URINE DOPAMINE

In a recent article in this journal (Brown & Dollery, 1981), we described the presence of DOPA in plasma in sufficient concentration to account for the free dopamine excreted in urine, and provided indirect evidence that decarboxylation of endogenous plasma DOPA does occur at a sufficient rate in the kidney. We concluded that this hypothesis could be tested by measuring the arterio-venous differences of DOPA and dopamine across the kidney, simultaneously with their excretion in urine; this evidence has now been obtained.

The subjects were six patients under investigation for a possible pheochromocytoma, in whom selective venous sampling was performed in the search for a localised source of catecholamine secretion. In these six patients, no such source was identified, and the diagnosis was also subsequently excluded by performance of the pentolinium suppression test (Brown *et al.*, 1981). All patients were mildly hypertensive (range 140/95-165/110), but had a normal urine sediment and creatinine clearance. In the sampling procedure, a venous catheter was intro-

duced via the femoral vein into both renal veins, under fluoroscopic control; on the left the catheter tip was 'upstream' of the adrenal vein. Blood (5 ml) was drawn from each vein together with simultaneous arterial samples from a femoral catheter. The patient's urine was collected from 1 h prior to the procedure for a total of 4 h. Samples were handled as described in our earlier report (Brown & Dollery, 1981). DOPA and dopamine were assayed radioenzymatically as before, with a recently described double-isotope modification which permits improved precision without loss of sensitivity (Brown *et al.*, 1981).

The arterial and renal venous concentrations of DOPA and dopamine and their urine excretion are shown in Table 1. This also gives the predicted renal vein DOPA concentration if urine free dopamine were entirely derived from renal decarboxylation of DOPA; renal blood flow has been calculated for each subject from body weight and height, using tables of normal values (Smith, 1951). The predicted figure is significantly lower than the observed concentration;

Table 1 The arterial and renal venous concentrations of (a) dopamine and (b) DOPA are shown for six subjects, together with their urine excretion; the renal vein concentrations are the mean for right and left. The 'predicted' renal vein DOPA concentration was calculated from the formula:

$$\text{Arterial DOPA concentration} - \frac{(\text{urine excretion of DOPA and dopamine})}{\text{estimated renal plasma flow}}$$

(a) Dopamine				
Subject	Urine excretion (nmol/h)	Arterial concentration (nmol/l)	Renal vein concentration (nmol/l)	
1	70.2	0.26	0.18	
2	43.2	0.16	0.11	
3	90.3	0.21	0.15	
4	82.8	ND	ND	
5	77.4	0.20	ND	
6	86.4	ND	ND	
(b) DOPA				
				'Predicted' renal vein concentration (nmol/l)
1	10.8	10.8	7.5	6.1
2	6.6	8.4	5.9	5.4
3	13.8	12.6	7.9	7.1
4	15.0	13.2	8.4	7.3
5	12.0	10.2	6.5	5.2
6	14.4	15.6	11.1	10.1
mean			7.8	6.9
s.d.			1.8	1.8

$P < 0.01$

ND not detected (< 0.10 nmol/l)

Statistical comparison was made by Student's paired *t*-test.

the mean arteriovenous difference of DOPA is 74% of the predicted difference if plasma DOPA were the sole precursor of urine dopamine.

This study confirms that DOPA is extracted by the kidney to a much higher degree than accountable by its urinary excretion (as DOPA). The extraction is consistent, however, with its conversion to urine free dopamine; this has also been recently demonstrated in micropuncture studies (Baines & Chan, 1980). Nevertheless, in the present study, the decarboxylation of DOPA could not account for all the urine dopamine. The increase in urine dopamine excretion described following salt loading has not been universally observed (Oates, Perkins & Lee, 1980). Since the only certain renal effect of dopamine receptor stimulation is renal vasodilation, which is a

cortical effect, it would not be clear how tubular production of dopamine (from decarboxylation of DOPA) would cause this. On the other hand, there is evidence of specific dopaminergic nerves in the renal cortex (Bell, Lang & Leska, 1978). It is possible that these make a minor, but physiologically important, contribution to urine dopamine.

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References

- BAINES, R.W. & CHAN, W. (1980). Production of urine free dopamine from DOPA; a micropuncture study. *Life Sci.*, **26**, 253-259.
- BELL, C., LANG, W.J. & LESKA, F. (1978). Dopamine-containing vasomotor nerves in the dog kidney. *J. Neurochem.*, **31**, 77-83.
- BROWN, M.J. & DOLLERY, C.T. (1981). A specific radio-enzymatic assay for dihydroxyphenylalanine (DOPA). Plasma DOPA may be the precursor of urine free dopamine. *Br. J. clin. Pharmac.*, **11**, 79-83.
- BROWN, M.J., ALLISON, D.J., JENNER, D.A., LEWIS, P.J. & DOLLERY, C.T. (1981). Increased sensitivity and

accuracy of phaeochromocytoma diagnosis achieved by plasma adrenaline estimations and a pentolinium suppression test. *Lancet*, i, 174-177.

OATES, N.S., PERKINS, C.M. & LEE, M.R. (1980). The effect

of mineralocorticoid administration on urine free dopamine in man. *Clin. Sci.*, 58, 78-82.

SMITH, H.W. (1951). *The Kidney: Structure and function in health and disease*. New York: Oxford University Press.

THE CYTOPROTECTIVE EFFECT OF 16,16-DIMETHYL-PROSTAGLANDIN E₂ ON BILE SALT INDUCED DAMAGE TO THE HUMAN STOMACH

Bile salts disrupt a 'gastric mucosal barrier' that normally serves to impede movement of H⁺-ions from the lumen into mucosa (Davenport, 1968). This barrier is defined in functional terms, and disruption of the barrier is said to have occurred when there is a fall in gastric transmucosal potential difference (p.d.). This drop in p.d. is presumably due to an increase in net flux of H⁺-ions out of the gastric lumen into the mucosa, usually accompanied by net flux of Na⁺-ions into the lumen (Kivilaakso & Silen, 1979). This increased H⁺-back-diffusion can induce gastric damage ranging from gastritis to frank ulceration in animal models (Ritchie & Cherry, 1979). In man, the reflux of bile acids into the gastric lumen has been considered as a possible factor in the aetiology of peptic ulceration and gastritis (Hoare *et al.*, 1978).

Certain prostaglandins protect the cells of the gastrointestinal epithelium in different laboratory animals from becoming inflamed and necrotic when the mucosa is exposed to bile salts and related noxious agents (Robert *et al.*, 1979). In detail, the degree of gastric ulceration in rats evoked by taurocholate could be markedly reduced by prior treatment with methylated prostaglandin analogues. This new property of prostaglandins was called 'cytoprotection' and is separate, and unrelated to the inhibition of gastric acid secretion (Robert, 1979).

Recently we have shown that 16,16-dimethyl-prostaglandin E₂ in very low, i.e. cytoprotective doses is able to prevent the aspirin-induced drop in

gastric transmucosal potential difference in man (Müller *et al.*, 1981). In the present study we have tested this prostaglandin analogue against sodium taurocholate in seven healthy volunteers by measuring the transmucosal potential difference, as originally described by Andersson & Grossman (1965).

Control and prostaglandin-experiments were carried out in the same subjects on separate days. P.d. recording was started after instillation of 100 ml of 0.9% saline to establish a basal control period of 15 min. The baseline p.d. averaged -37.2 ± 4.60 mV. Intragastric administration of 1.0 µg of 16,16-dimethyl-prostaglandin E₂ did not alter baseline p.d. over a period of 15 min when compared to vehicle control (-39.1 ± 4.75 mV). Sodium taurocholate (50 ml of 4 mmol/l, pH 7.4) when instilled without prostaglandin pretreatment reduced the intragastric p.d. by about 35% within 10 min (mean p.d. -25.3 ± 4.13 mV). After this reduction p.d. gradually recovered to -34.6 ± 9.95 mV over a time period of further 15 min. In contrast, 1.0 µg of 16,16-dimethyl-prostaglandin E₂ completely prevented this sodium taurocholate-evoked fall in gastric p.d. (Table 1). Doses below 1.0 µg which were proven to be effective against aspirin (Müller *et al.*, 1981), only partially inhibited this p.d. decrease by taurocholate.

In conclusion, this study demonstrates that 16,16-dimethyl-prostaglandin E₂ in low doses also protects gastric mucosa against sodium taurocholate injury in man. The finding that this prostaglandin analogue

Table 1 Human gastric potential difference after sodium taurocholate (50 ml, 4 mmol/l) with and without pretreatment with 16,16-dimethyl-prostaglandin E₂ over 15 min. (Control and prostaglandin-experiments were carried out on separate days, each subject serving as his/her own control)

	Controls	16,16-dm-PG E ₂	Sodium taurocholate (after 10 min) with 16,16-dm PG E ₂	without
P.d. (-mV)	37.2 ± 4.6	39.1 ± 4.7	39.1 ± 4.1*	25.3 ± 4.1

Data represent mean values ± s.d.

* $P < 0.05$ (Wilcoxon-test for paired observations in comparison with the untreated group)