was sufficient to account for the observed hydrolysis. Whether the hydrolysis is intracellular or intravascular (Robertson & others, 1972) the entry of the intact benorylate molecule into mucosal cells appears to be an important step in the absorptive mechanism. The physicochemical form of presentation of intact benorylate at the mucosal cells would therefore be an important factor in the rate of its absorption into cells.

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# The effect of ticarcillin on the haemostatic mechanism

Ticarcillin (disodium-α-carboxy-3-thienyl methyl penicillin) is a new semi-synthetic antibiotic with a structure and spectrum of antibacterial activity similar to that of carbenicillin (disodium-α-carboxy benzyl penicillin). It is as active as carbenicillin against *E. coli*, *Enterobacter* and indole-positive proteus species, but has at least a two fold greater activity against strains of *Pseudomonas aeruginosa* (Neu & Winshell, 1970; Sutherland, Burnett, & Robinson, 1971; Lynn, 1973). Adverse effects on the haemostatic mechanism have been reported during carbenicillin treatment when serum concentrations of the drug are of the order of 200 $\mu$g ml$^{-1}$. Such effects include the onset of a haemorrhagic diathesis (Gordon, 1970; Lurie & Goldberg, 1970; Waisbren, Evani & Ziebert, 1971; Yudis, Mahood & Maxwell, 1972; Brown, Natelson & others, 1974; Demos, 1971), prolongation of the thrombin, prothrombin, kaolin cephalin clotting time and bleeding time (Lurie, Gold & others, 1970) and depressed platelet aggregation to ADP (McClure, Casserly & others, 1970; Lederer, Davies & others, 1973) both *in vivo* and *in vitro*. In view of the reported effects of carbenicillin on the haemostatic mechanism, and the structural similarity and usage of ticarcillin, the *in vivo* and *in vitro* effects of ticarcillin on the haemostatic mechanism have been investigated.

Procedures for coagulation and fibrinolytic assays have been described previously (Lederer & others, 1973). Serum concentrations of ticarcillin were estimated by a microbiological assay using *Pseudomonas aeruginosa* as test organism.

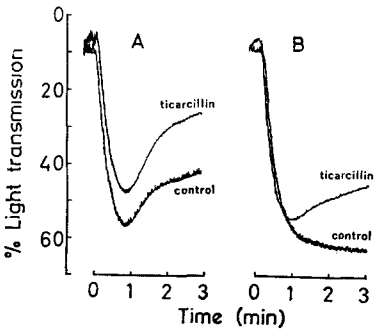


FIG. 1. The *in vitro* effect of ticarcillin (1280 $\mu$g ml$^{-1}$) on ADP-induced primary and secondary platelet aggregation. A—2 $\mu$M ADP, B—4 $\mu$M ADP.

In *in vitro* studies ticarcillin was added to normal plasma or platelet-rich plasma to give final concentrations of 20, 40, 80, 160, 320, 640, and 1280 $\mu$g ml$^{-1}$. The drug had no effect on thrombin time, prothrombin time, activated partial thromboplastin time, fibrinogen or plasminogen concentration, platelet factor 3 availability or euglobulin lysis with or without a 2 h preincubation at 37°. However, at a concentration of 1280 $\mu$g ml$^{-1}$, the antibiotic inhibited both primary and secondary platelet aggregation to ADP (Fig. 1) after a 2 h pre-incubation at 37°. The drug was without effect at the lower concentrations and did not affect platelet aggregation induced by adrenaline or collagen.

Infusion of 5 g ticarcillin in sterile saline into 6 normal volunteers resulted in serum concentrations of ticarcillin of 190 $\pm$ 23 and 30 $\pm$ 5 $\mu$g ml$^{-1}$ (mean $\pm$ s.e.), 30 min and 4 h post-infusion respectively. Following the infusion no changes occurred in prothrombin time, plasminogen concentration, bleeding time, platelet adhesiveness, platelet factor 3 availability or platelet aggregation to ADP, adrenaline or collagen. Small decreases in both thrombin time and activated partial thromboplastin time of plasma were seen 4 h after antibiotic administration in five of the six subjects. Thrombin time decreased from a pre-infusion mean ($\pm$ s.e.) of 17·6 $\pm$ 0·5 s to 17·2 $\pm$0·5 s and the activated partial thromboplastin time from 40·4 $\pm$ 1·9 to 36·7 $\pm$ 2·1 s. These changes were statistically significant ($P<0{\cdot}025$; paired $t$ test). Each of the six

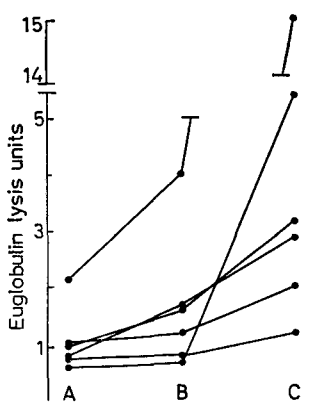


FIG. 2. The effect of ticarcillin (5 g) infusion in 6 volunteers on euglobulin lysis. Euglobulin lysis activity expressed in units as a reciprocal of the lysis time, one unit corresponding to a lysis time of 300 min. A—preinfusion, B—post infusion (0·5 h), C—post infusion (4 h).

subjects showed increased euglobulin lysis activity (Fig. 2) following ticarcillin infusion, increasing from the pre-infusion mean (± s.e.) of 1·03 ± 0·23 to 1·64 ± 0·51 units at 30 min and to 4·94 ± 2·10 units at 4 h post-infusion.

The results indicate that, at the same dosage level, ticarcillin is less effective than carbenicillin in its inhibition of platelet function, the latter having been shown in a previous and similar study (Lederer & others, 1973) to inhibit ADP-induced aggregation *in vitro* over a 20–1280 $\mu$g ml$^{-1}$ concentration range and to cause inhibition of platelet aggregation in volunteer subjects. Levels of administration of ticarcillin have been suggested for therapy in patients with chronic renal failure undergoing dialysis in order to maintain a therapeutically effective serum concentration of 50 $\mu$g ml$^{-1}$ (Wise, Reeves & Parker, 1974). Increases in euglobulin lysis activity consequent on ticarcillin administration observed in the present study are greater than would be expected as a consequence of diurnal variation (Fearnley, Balmforth & Fearnley, 1957) than observed over a similar time period in subjects receiving no drug therapy, (Davies, Lederer & others, 1974) and than observed in volunteers following carbenicillin infusion (Lederer & others, 1973).

It is considered that the observed effects of ticarcillin on blood coagulation, platelet function and fibrinolysis would be unlikely to impair haemostasis when ticarcillin is employed at the concentration used in the present study. Such effects, may, however, be of importance in the presence of uraemia, in which impaired renal clearance may result in high plasma concentrations of the drug and in which pre-existing disorders of platelet function may be present (Stewart & Castaldi, 1967; Eknoyan, Wacksman & others, 1969; Rabiner & Hrodek, 1968).

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