Time

15.15 **0173** CARBENICILLIN AND PENICILLIN G IMPAIR PLATELET FUNCTION BY INHIBITING THE BINDING OF AGONISTS TO THE PLATELET SURFACE

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Carbenicillin (carb) and penicillin G (pen) inhibit human platelet function in vivo and can cause a bleeding diathesis. Since the mechanism by which these drugs inhibit platelets is unknown, we investigated whether they might interfere with the binding of epinephrine, ADP, or ristocetin (von Willebrand factor) to the platelet surface in vitro. Pen (10 mM) or carb (20 mM) produced a 6-fold decrease in the affinity of receptors on intact platelets for both epinephrine and for the α-adrenergic antagonist, ^{3}H-dihydroergocryptine ($p < 0.001$). Neither antibiotic changed the maximum number of α-adrenergic binding sites per platelet. Pen and carb at these concentrations completely inhibited ^{14}C-serotonin release induced by 1 μM epinephrine and inhibited primary platelet aggregation by 50%. Similarly, these antibiotics inhibited aggregation and serotonin release induced by 1 μM ADP and inhibited the covalent binding of an ADP analogue ($5'FSO_2B_Z$Ado) to its specific binding protein in platelet membranes. Moreover, pen and carb inhibited competitively the agglutination of platelets by ristocetin. Thus, carbenicillin and penicillin G decrease the affinity of a number of distinct platelet receptors for their specific agonists, and this correlates with inhibition of platelet function induced by these agonists. Interaction of these antibiotics with the platelet surface membrane may account for their hemorrhagic as well as their anti-thrombotic activity.

15.30 **0174** HUMAN PHARMACOLOGY STUDIES IN VOLUNTEERS WITH INDOBUFEN (K 3920), INHIBITOR OF PLATELET AGGREGATION

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Given by the i.v. route to healthy volunteers, indobufen has an half-life of 7-9 h. After oral administration of tablets, the drug is completely absorbed. Excretion occurs through the kidney and the drug is present in the urine as glucuronide and in unchanged form. The maximum inhibitory effect on collagen-induced platelet aggregation was observed 1 to 4 h after i.v. and p.o. administration but activity at 8 h was more marked after p.o. administration in accordance with the higher plasma levels found at that time. During repeated administration at the dose of 100 mg b.i.d. for 7 days, no important changes in kinetic parameters and activity of indobufen was observed. Indobufen is rapidly absorbed also when given by the i.m. route, giving at 30 min peak levels comparable to those observed after oral administration. These data suggest that indobufen is active by the i.v., p.o. and i.m. routes, that its effect on platelets, unlike ASA, is reversible, and that its kinetics is linear.

15.45 **0175** INHIBITION OF LEUKOCYTE ADHESION AND MIGRATION IN CANINE JUGULAR VEINS BY A SLOWLY METABOLIZED DERIVATIVE OF LIDOCAINE (TOCANIDE).

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Local dissection followed by brief stasis caused massive adhesion to and invasion of medium sized veins of dogs, rabbits and humans by polymorphonuclear neutrophils (PMN). In dogs both were inhibited by intravenous lidocaine (Am. J. Pathol., 74:507). Inhibition of PMN adhesion and invasion by tocanide, a primary amine derivative of lidocaine (2-amino-2,6-propionoxylidide, Astra Pharmaceutical Co.), with a biological half life of 10-12 hours was quantitated with ^{111}In-labeled leukocytes. Canine jugular veins were freed from surrounding tissue and side branches ligated. After 3-hour intravenous infusion of saline (control) or tocanide (0.7 mg/kg/minute for 20 minutes followed by 0.07 mg/kg/minute for 2 hours 40 minutes) jugular were occluded for 5 minutes, cannulated and washed free of nonadhering blood elements before removal for counting of radioactivity and examination of scanning electron microscopy. In one group tocanide was started before, and the other group after neck dissection and injection of ^{111}In-leukocytes (dissection and stasis provided stimulus for attraction of PMN). Vessel and blood counts were standardized to give blood equivalents of PMN per gram of vessel. Results were: Controls, 0.92 ml/gm; tocanide started after dissection, 0.54 ml/gm; and tocanide started before dissection, 0.12 ml/gm. SEM showed typical adhesion and invasion by PMN. Plasma levels of tocanide were 2-4 μM. Thus, tocanide inhibited the PMN component of inflammation by 46-87% depending on regimen.