Trimethoquinol is a potent prostaglandin endoperoxide antagonist

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Trimethoquinol (TMQ, Ro 07-5965; Roche) has an inhibitory effect on 'secondary' platelet aggregation that is reminiscent of that of aspirin but it does not inhibit platelet prostaglandin (PG) production, or elevate platelet cyclic AMP levels (Shtacher, Crowley & Dalton, 1976). Possible explanations for the effects of TMQ were inhibition of platelet thromboxane (TX) synthesis, or blockade of platelet receptors for dienoic PG endoperoxides (and/or TXA_2). We have now obtained evidence for the latter possibility.

Agents tested (Gordon & Drummond, 1974) on platelet aggregation were: ADP (Sigma); arachidonic acid (Sigma); 15α-hydroxy-9α,11α (methanoepoxy)-prosta-5*cis*,13*trans*-dienoic acid (U46619, Upjohn); 15α-hydroxy-9α,11α (epoxymethano)prosta-5*cis*,13-*trans*-dienoic acid (U44069, Upjohn); 15α-hydroxy-9α,11α-azo-prosta-5*cis*,13*trans*-dienoic acid (Azo-PGH_2, kindly supplied by Prof. E.J. Corey); PGG_2 and PGH_2 [Ran Biochemicals (Israel), or prepared by the method of Willis, Vane, Kuhn, Scott & Petrin (1974)].

Thromboxane A_2 was generated from PGH_2 or PGG_2 by platelet microsomes and detected by platelet aggregation or contractions of isolated aorta of rabbit (Needleman, Moncada, Bunting, Vane, Hamberg & Samuelsson, 1976). Rabbit aorta was also used to examine effects of TMQ on the vasoconstrictor actions of endoperoxides and TXA_2.

Trimethoquinol potently inhibited aggregation induced by natural dienoic endoperoxides, endoperoxide analogues, arachidonic acid and TXA_2, although 'primary' aggregation induced by ADP was not reduced (Table 1). Contractions of rabbit aorta induced by PGH_2, but not TXA_2, were also suppressed by TMQ at 10 μg/ml. Pre-incubation of platelet microsomes with TMQ (10–100 μg/ml) for up to 4 min (at 0°C) did not suppress production of TXA_2-like activity. Hence, the anti-aggregatory effects of TMQ may involve blockade of at least two receptor sites, since MacIntyre & Gordon (1977) previously obtained evidence that the endoperoxides and TXA_2 act at different platelet receptors. Our results indicate that there are also distinct endoperoxide and TXA_2 receptors in vascular tissue, and that the former is more susceptible to inhibition by TMQ.

Table 1 Results are mean values from a minimum of three separate experiments using platelet-rich plasma from different donors. The IC_{50} concentration of TMQ is that which inhibits amplitude of the aggregation response by 50%

Aggregating agent (and concentration in μM)	*TMQ IC_{50} μg/ml*	*μM*
PGH_2 (0.2–2 μM)	<0.5	<1.4
PGG_2 (0.2–1 μM)	0.2	0.56
U46619 (1.0)	0.1	0.28
U44069 (1.0)	0.1	0.28
Azo-PGH_2 (2.0)	0.2	0.56
Arachidonic acid (300)	1.0	2.8
TXA_2 (generated from <1.0 μM PGG_2)	1.0	2.8
ADP (1.0)	100	280

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