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Use of desmopressin to prevent bleeding complications in patients treated with aspirin

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Aspirin induces a haemorrhagic diathesis that persists for at least 1 week after discontinuation of the drug. The effect of the vasopressin analogue desmopressin was studied in 12 patients treated with aspirin who were undergoing cholecystectomy. Desmopressin was given to six of these patients. There were five postoperative bleeding complications; all occurred in patients who had not received desmopressin ($P < 0.05$). *The bleeding time was prolonged in aspirin-treated patients and normalized by desmopressin* ($P < 0.05$). *Desmopressin can be used safely to prevent bleeding induced by aspirin.*

Aspirin is one of the most widely used drugs in the world and is increasingly employed in the prevention of cardiovascular disease. Other non-steroidal anti-inflammatory drugs with principally the same mode of action are widely used as analgesics. The effect of these drugs in the inhibition of platelet function[1] is of increasing concern.

Desmopressin ([1-deamino-8-D-arginine]vasopressin) is a synthetic analogue of vasopressin without vasopressor activity. It induces the release of coagulation factor VIII, von Willebrand factor and tissue plasminogen activator from the endothelium. It is used to achieve appropriate haemostasis in patients with mild forms of haemophilia A and von Willebrand's disease who undergo surgery. Moreover, desmopressin is effective in uraemia, liver cirrhosis and several other conditions associated with defects of platelet function[2].

The aim of this study was to investigate the effect of desmopressin on aspirin-induced prolongation of bleeding time and blood loss in patients undergoing surgery.

Patients and methods

Patients

Eighteen patients undergoing elective cholecystectomy were studied (*Table 1*). They were all non-obese, without a history of bleeding episodes or thrombotic events, and with normal liver function, serum lipid and blood glucose levels. Informed consent was obtained from each patient before operation. The protocols were approved by the committee of ethics at Karolinska Institute. The administration of desmopressin was approved by the National Swedish Board of Health.

Drug administration

Six patients received aspirin (Dispril; Meda, Göteborg, Sweden), 500 mg twice daily for 5 days, taking the last dose on the evening before surgery. Six patients were given desmopressin (Minirin; Ferring, Malmö, Sweden) and aspirin as above. Desmopressin (0·3 μg per kg body-weight) was given twice – just before the induction of anaesthesia and 6 h later – and was infused intravenously over 20–30 min. Six patients were included as untreated controls and received neither aspirin nor desmopressin.

Anaesthetic and surgical procedure

Anaesthesia was induced with fast-acting barbiturate and maintained with fentanyl, nitrous oxide and enflurane during muscle relaxation and endotracheal intubation. Cholecystectomy was performed via a right subcostal incision. Intercostal blockade with bupivacaine and intramuscular injection of ketobemidone was used for postoperative pain relief. Pharmacological prophylaxis of thrombosis was not used.

Bleeding parameters

The bleeding time was determined according to a modification of Ivy's method, with the Surgicutt device (Ortho Diagnostic Systems, Edison, New Jersey, USA) and 40 mmHg stasis (normal range 1·8–7·0 min). This was carried out before and after both doses of desmopressin. In control patients the determination was made before surgery and 6 h later. Intraoperative blood loss was recorded. After operation a bleeding episode was recorded when the wound dressings had to be renewed because of bleeding. Circulatory instability with a significant fall in haemoglobin level for no apparent reason was also considered to indicate a postoperative bleeding episode.

Table 1 *Details of 18 patients* undergoing cholecystectomy*

	Aspirin ($n=6$)	Aspirin plus desmopressin ($n=6$)	Control ($n=6$)
Sex ratio (M:F)	2:4	2:4	1:5
Mean(s.d.) age (years)	55(9)	48(11)	51(8)
Mean(s.d.) operation time (min)	120(76)	91(47)	83(37)
Mean(s.d.) intraoperative blood loss (ml/h)	159(94)	86(87)	86(83)
Postoperative bleeding episodes	5†	0‡	0
Blood transfused (units)	4	0	0
Mean(s.d.) preoperative bleeding time (min)		7·4(1·2)†	5·0(2·2)
After desmopressin		5·5(0·8)§	
Mean(s.d.) postoperative bleeding time (min)		5·9(0·7)	5·0(1·1)
After desmopressin		3·9(0·7)§	

*Twelve patients received aspirin for 5 days before surgery and six of these were given desmopressin before and after operation. †$P < 0.05$ (*versus* control, Mann–Whitney U test); ‡$P < 0.05$ (*versus* aspirin alone, Mann–Whitney U test); §$P < 0.05$ (*versus* before desmopressin, Wilcoxon signed rank test)

Statistical analysis

Comparisons were carried out using the two-tailed Mann–Whitney U test and the Wilcoxon signed rank test[3].

Results

The mean preoperative bleeding time in patients receiving aspirin was prolonged to 7·4 min, compared with a mean in control patients of 5·0 min ($P < 0.05$) (*Table 1; Figure 1*). Each dose of desmopressin significantly reduced the bleeding time ($P < 0.05$), which remained within the normal range after the first desmopressin infusion.

There were five postoperative bleeding episodes, all in patients receiving aspirin alone (*Table 1*). Four patients had bleeding from the wound requiring a change of dressing and the fifth episode was noted when a patient experienced vertigo and had a haemoglobin level of 8·3 g/dl on the third day after operation (preoperative level 13·9 g/dl, intraoperative blood loss 250 ml). In the control and desmopressin plus aspirin

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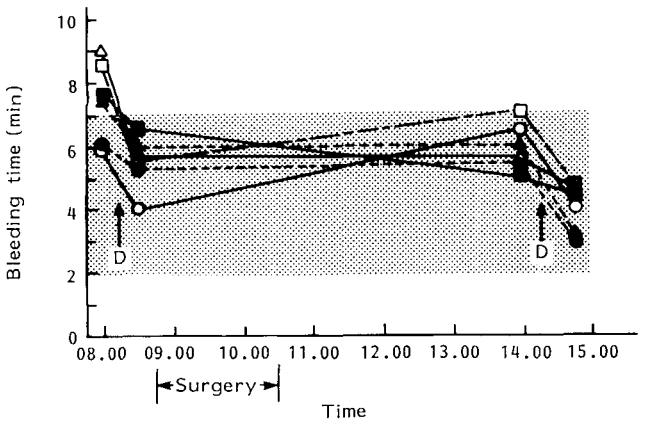

Figure 1 *Bleeding times in six patients undergoing cholecystectomy who were treated with aspirin plus desmopressin.* ▨, *Normal range; D, desmopressin infusion*

groups there were no postoperative bleeding episodes. The difference was statistically significant ($P < 0{\cdot}05$).

All patients had facial flushing without discomfort for 15–30 min after the first desmopressin dose, but none after the second. No other side-effects attributable to desmopressin were noted.

Discussion

Aspirin-treated patients undergoing cholecystectomy had a haemorrhagic diathesis, as shown by a prolonged bleeding time and high incidence of bleeding episodes after surgery. Desmopressin prevented bleeding complications and normalized the bleeding time in such patients. This is in accordance with previous studies, which have shown that desmopressin normalizes the prolongation of bleeding time induced by aspirin in volunteers[4,5] and aspirin-treated patients not undergoing surgery[6,7]. The use of desmopressin to achieve normal surgical haemostasis after aspirin ingestion has previously been reported in a single case[6]; this, however, is the first report of a series.

Aspirin irreversibly inhibits the transformation by cyclo-oxygenase[1] of arachidonic acid into prostacyclin and thromboxane A_2. Prostacyclin, synthesized mainly in the vascular endothelium, is an inhibitor of platelet adhesion. In the presence of higher levels of aspirin, prostacyclin synthesis is depressed; at lower levels, synthesis recovers. Thromboxane A_2, formed mainly in platelets, promotes platelet adhesion. The synthesis of thromboxane A_2 cannot recover after aspirin administration because of the irreversible inactivation of cyclo-oxygenase; mature platelets have no nuclei and cannot, therefore, synthesize protein[1]. Thus, aspirin inhibits platelet function because it inactivates synthesis of proaggregatory thromboxane A_2 for the rest of the life of the platelet (about 10 days on average), but leaves the production of antiadhesive prostacyclin largely unaffected.

Thromboxane synthesis does not recover after desmopressin administration. The mechanism of its effect in aspirin-induced platelet dysfunction involves the release of larger than normal von Willebrand multimers, which are particularly effective in binding platelets to subendothelial collagen[2].

The bleeding time determination made after the first desmopressin dose may have underestimated the effect of the drug. It was carried out immediately after a 20-min infusion, but the peak of the von Willebrand factor increase is not achieved until 1–2 h after infusion[2]. Moreover, the rapid infusion of the first dose caused obvious temporary dermal vasodilatation in all patients, and the blood flow during that bleeding time determination was about fivefold greater than during all others. This increased blood flow may have flushed away platelet aggregates, making the bleeding time inaccurately prolonged.

No adverse effects were noted, apart from short-lasting facial flushing after the first dose. There are reports of patients in whom coronary artery thrombosis was suspected, and it has been recommended that desmopressin be used cautiously in those with atherosclerosis[8]. However, the number of reported cases has been only 1 per 50 000 patients treated[9]. In a review of all studies of patients undergoing cardiopulmonary bypass surgery, there was the same incidence of thrombotic events in desmopressin- and placebo-treated patients[9]. There is no evidence of an increased risk of venous thrombosis[10] or of disturbances of water–electrolyte balance in patients undergoing surgery[11].

It is concluded that desmopressin normalizes aspirin-prolonged bleeding time in patients undergoing surgery. This is the first study to show a simple and uncomplicated way of preventing the surgical bleeding complications induced by a non-steroidal anti-inflammatory drug.

References

1. Verstraete M, Kienast J. Pharmacology of the interaction between platelets and vessel wall. *Clin Haematol* 1986; **15**: 493–508.
2. Schulman S. DDAVP – the multipotent drug in patients with coagulopathies. *Transfusion Medicine Reviews* 1991; **V**: 132–44.
3. Siegel S, Castellan NJJ. *Nonparametric Statistics for the Behavioral Sciences*. 2nd ed. Singapore: McGraw-Hill, 1989.
4. Mannucci PM, Vicente V, Vianello L *et al.* Controlled trial of desmopressin in liver cirrhosis and other conditions associated with a prolonged bleeding time. *Blood* 1986; **67**: 1148–53.
5. Lethagen S, Rugarn P. The effect of DDAVP and placebo on platelet function and prolonged bleeding time induced by oral acetyl salicylic acid intake in healthy volunteers. *Thromb Haemost* 1992; **67**: 185–6.
6. Kobrinsky NL, Israels ED, Gerrard JM *et al.* Shortening of bleeding time by [1-deamino-8-D-arginine]vasopressin in various bleeding disorders. *Lancet* 1984; **i**: 1145–8.
7. Schulman S, Johnsson H, Lindstedt M. Desmopressin as a haemostatic agent in patients with disorders of primary haemostasis. *Eur J Surg* 1991; **157**: 647–52.
8. Editorial. Desmopressin and arterial thrombosis. *Lancet* 1989; **i**: 938–9.
9. Mannucci PM, Lusher JM. Desmopressin and thrombosis. *Lancet* 1989; **ii**: 675–6.
10. Flordal PA, Ljungström K-G, Fehrm A. Desmopressin and postoperative thromboembolism. *Thromb Res* 1992; **68**: 429–33.
11. Flordal PA, Ljungström K-G. Effects of high dose desmopressin and dextran on renal function and blood volume. A study in normal subjects and in patients undergoing total hip replacement. *Acta Anaesthesiol Scand* 1993; **37**: 1–6.

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