Activité de l'aspirine à dose ultra faible sur l'interaction plaquette-paroi vasculaire

Travaux réalisés par l'équipe du Pr Doutremepuich
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Étude de différentes doses d'aspirine dans un modèle de thrombose induit par laser chez le rat

Vesvers et coll. Haemostasis 1993

Doutremepuich et coll. Thromb Res 1994

Doutremepuich et coll. Semin Thromb Hemost 1996

Méthodes

Nouveau modèle d'étude de l'agrégation plaquettaire *in vivo*.

Formation d'une thrombose grâce à un faisceau laser qui détruit quelques cellules de l'intima d'une artériole.

Enregistrement vidéo automatique :

- du nombre de tirs laser nécessaires,
- de la surface et la durée du thrombus,
- de la durée d 'embolisation et du nombre d'emboles.

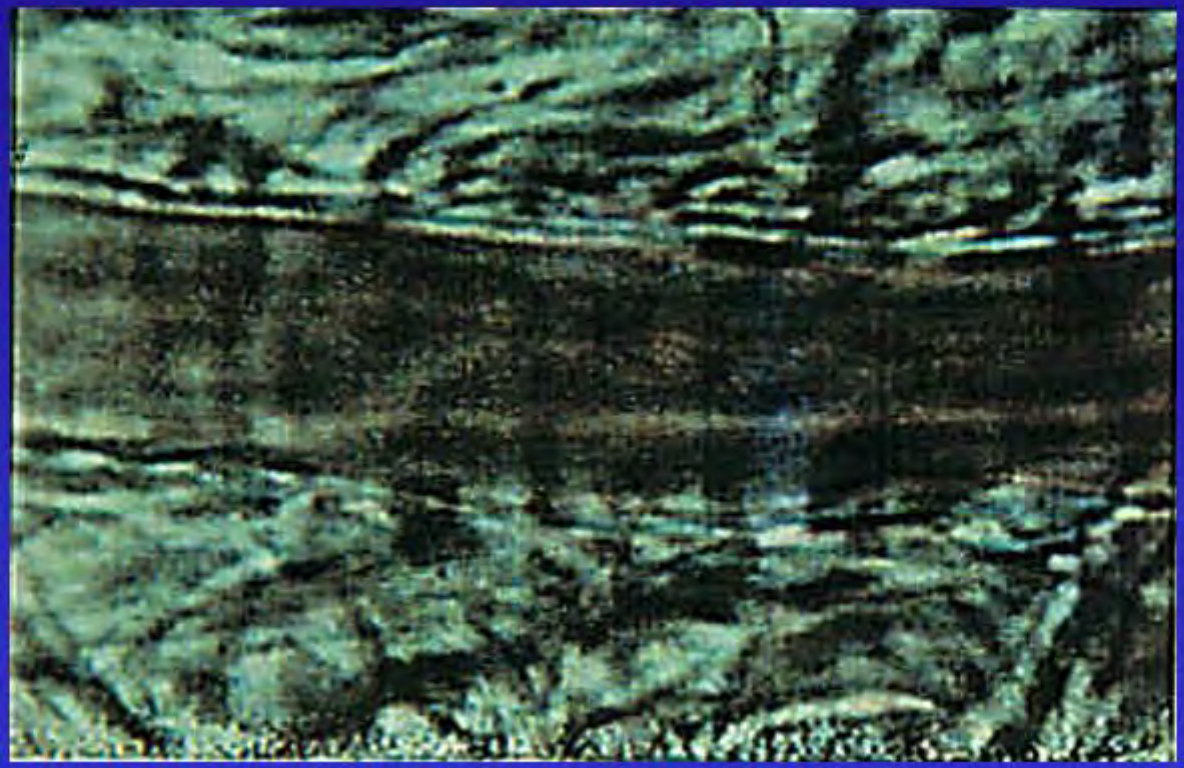
Mesure de la fonction plaquettaire et du temps de saignement

Méthodes

- Effet de l'aspirine administrée avant la thrombose
- Administration d'aspirine à différentes concentrations (100 mg/kg à 30 CH soit 10^{-60} mg/kg),
- Groupes contrôles
  1 .Traité au sérum physiologique,
  2. Traité au salicylate (100 mg/kg)

Résultats :
images du thrombus obtenu

Artériole mésentérique avant la lésion



Résultats :
images du thrombus obtenu

Le même vaisseau pendant l'application du laser

Résultats :
images du thrombus obtenu

Le même vaisseau 3 secondes après

Formation d'un thrombus au lieu de la blessure par le laser.

Résultats :
images du thrombus obtenu

Le même vaisseau 30 secondes après

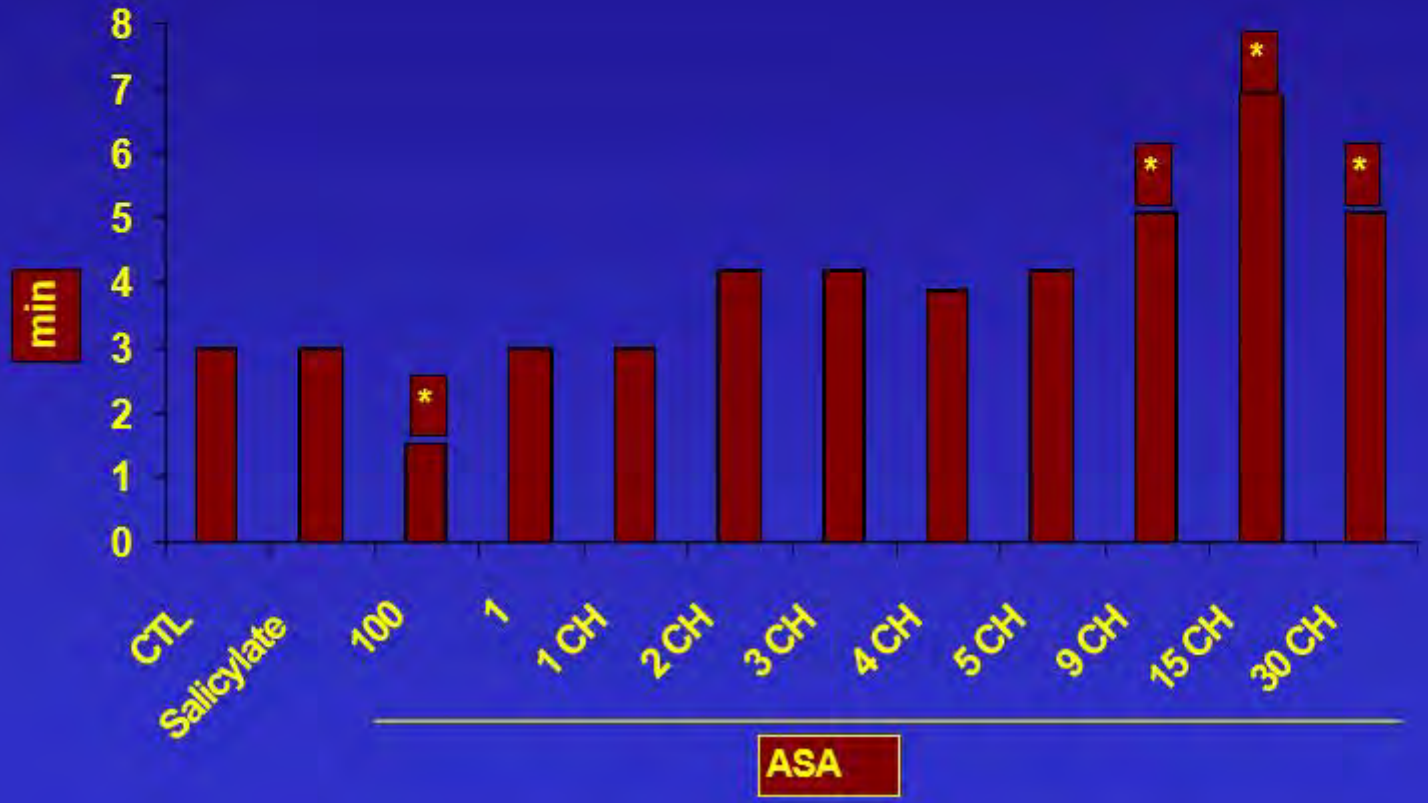
Le thrombus occupe presque toute la lumière artériolaire.

Émission d'emboles.

Résultats :

Effets des différentes concentrations d'aspirine

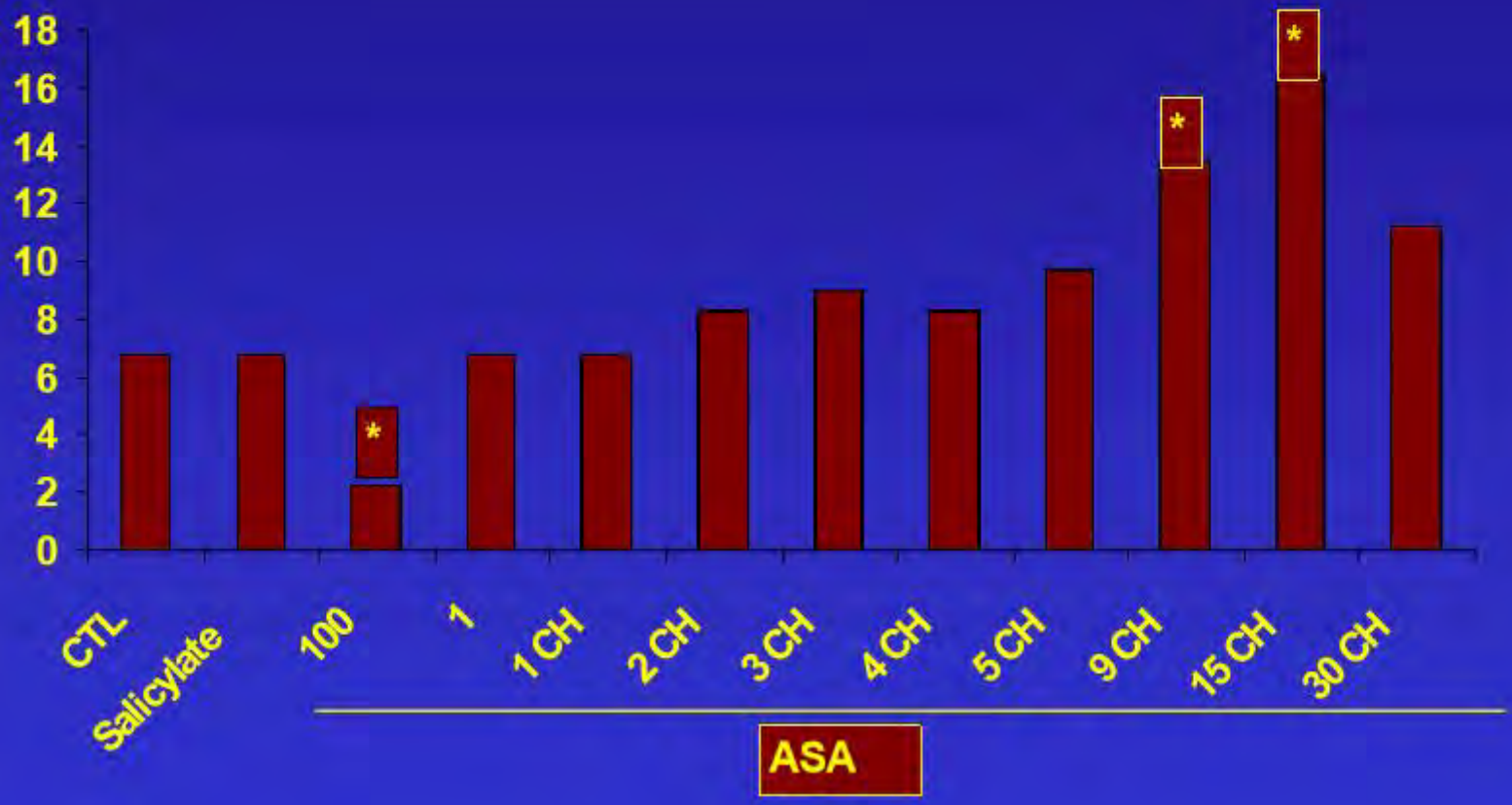
Durée de la thrombose :



Résultats :

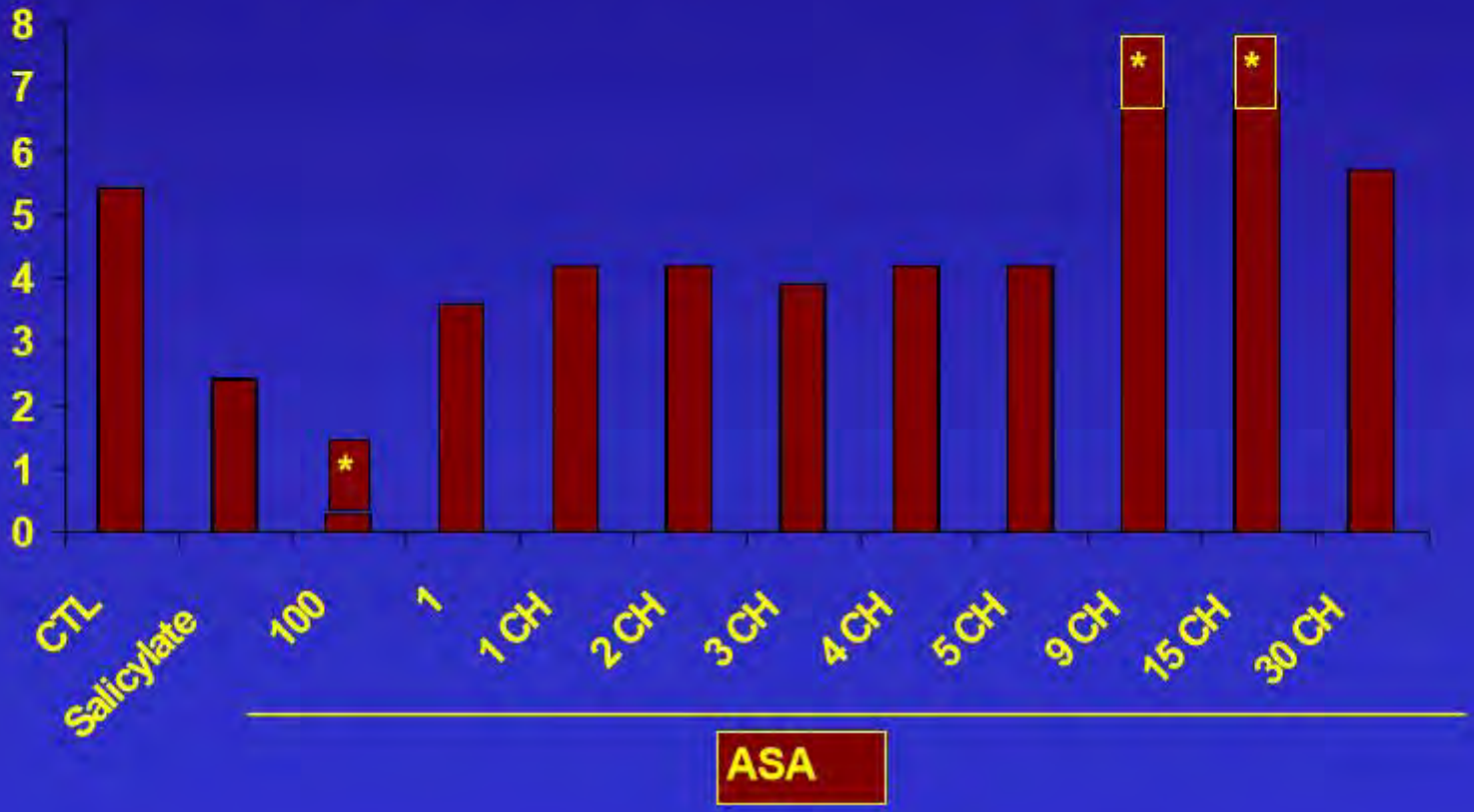
Effets des différentes concentrations d'aspirine

Nombre d'emboles :



Résultats :
Effets des différentes concentrations d'aspirine

Amplitude de l'agrégation plaquettaire :



Conclusion

L'aspirine 100 mg/kg présente bien une action anti-agrégante et anti-thrombotique.

Aux très faibles doses (9, 15, 30 CH avec un maximum en 15 CH), elle est pro-agrégante, pro-thrombotique.

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THROMBOSIS RESEARCH

ORIGINAL ARTICLE

Time Related Neutralization of Two Doses Acetyl Salicylic Acid

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Abstract

Aspirin has a well established role in the prevention of arterial thrombosis. Discussion on the efficacy and safety of aspirin in the treatment and prophylaxis of thrombosis has become an important issue. In fact, hemorrhage complications are often associated with its use. On the other hand, previous studies showed unexpected thrombotic potencies associated with the presence of this drug at ultra low doses (ULD) in the circulation. In this study, we aimed to evaluate the effect of aspirin at ULD, injected 1, 2, or 3 hours after the administration of aspirin at 100 mg/kg, on hemostasis and bleeding in rats. We used an experimental model of thrombosis induced by laser beams to evaluate these effects. Platelet aggregation was determined by Cardinal and Flower method. Results from this investigation demonstrate that the neutralizing effect of aspirin at ULD did not operate significantly 1 hour after the injection of aspirin at 100 mg/kg. This effect was observed 2 and 3 hours after. The use of aspirin at ULD to neutralize the side effects of aspirin at high doses will reduce the hemorrhagic risk during extra corporeal circulation. The therapeutic benefit and safety of aspirin therapy in the treatment of cardiovascular diseases can be obtained.

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Key Words: Thrombosis; Aspirin; ULD; Neutralization; Hemorrhage

Long-term treatment with aspirin is recommended for patients with large-vessel peripheral arterial disease since these patients have a high risk of death from cardiovascular causes.

The antithrombotic action of aspirin (ASA) is due to inhibition of platelet function by acetylation of the platelet cyclooxygenase at the functionally important amino acid serine 529. It prevents access of the substrate (arachidonic acid) to the catalytic site of enzyme at Tyrosine 385 and results in an irreversible inhibition of platelet-dependent thromboxane formation.

Aspirin inhibits platelet and endothelial cyclooxygenase. Its antithrombotic effect has been ascribed to the ability of endothelial cells to synthesise new enzyme in contrast to platelets which are anuclear [1] and also to presystemic inhibition of platelets [2]. In fact, the anti-thrombotic effect of aspirin at current doses is well known since it is largely demonstrated. It is widely used to prevent arterial thrombosis, cerebral strokes [3] or myocardial infarction [4,5], and to reduce the risk of death in patients. The optimum dose of aspirin as an anti-thrombotic drug can differ in different organ circulation. While 100 mg/day is sufficient for prevention of thrombus formation in the coronary circulation, higher doses may be required for the prevention of vascular events in the cerebral and peripheral circulation. However, any effective antiplatelet dose of aspirin is associated with an increased risk of bleeding. Therefore, the individual

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Aspirin at Very Ultra Low Dosage in Healthy Volunteers: Effects on Bleeding Time, Platelet Aggregation and Coagulatic

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Key Words. Aspirin · Bleeding time · Platelet aggregation · Coagulation test

Abstract. Aspirin at very ultra low dosage was tested in healthy volunteers (n = 20) in randomized, double-blind and placebo-controlled trial. The results showed a bleeding tir reduction ($p < 0.05$) in volunteers having previously ingested aspirin. Platelet aggregati on platelet-rich plasma was not statistically modified after aspirin ingestion. Thrombin cl ting time was always higher ($p < 0.05$) in the treated group.

Introduction

At low dosage, aspirin is known to diminish platelet aggregation, mainly by TXA_2 synthesis inhibition and to prolong bleeding time [1]. When aspirin is ingested at very ultra low dosage, bleeding time used to reflect in-vivo physiological platelet functions is markedly reduced. This previous observation [2, 3] made on healthy volunteers was quite new. No simple explanation could be given and it seemed that only one test was not sufficient to reflect the mechanism of action of aspirin at very ultra low dosage.

The present study employed in vitro as well as in vivo techniques. It was performed in rigorous conditions in order to eliminate potential modifying parameters like sex or stress [4, 5] and to demonstrate that such dosage does not give a placebo response.

Materials and Methods

Drugs

Aspirin dilutions (batches No. 4416 and 44 were prepared by Boiron laboratory (Ste-Foy-L Lyon, France) as follows: 1 g of pure, finely powde aspirin was suspended in 99 ml of alcohol (70°); solution was vigorously shaken to obtain a first di tion. Then 1 ml of this dilution was mixed in 99 m distilled water; after vigorous shaking, a second di tion was obtained.

The process was then repeated to the fifth di tion, which was kept for the study. This dilution c tained $334 \cdot 10^9$ molecules/ml solution.

The placebo solution was distilled water (batc No. 4415 and 4419). These products were identif only by a code given by an independent person.

Healthy Volunteers

Twenty healthy male volunteers (mean age = 2 ± 5.7 years) were included in this double-blind t after obtaining their informed consent. These patie had no aspirin allergy or coagulation disorders a