دراسة مختبرية للمركبات 3-(استيل سالسويل)- 6،5 -o - ايزوبروبليدين-

فراس طاهر ماهر ،عبد الجبار عبد القادر مخلص ،عدنان ابراهيم عبود* ،نزار احمد ناجي**
قسم الكيمياء ،كلية التربية -ابن الهيثم ، جامعة بغداد
* وزارة العلوم والتكنلوجيا
*كلية العلوم ،جامعة تكريت

الخلاصة

اجريت دراسة في داخل جسم الكائن الحي (Invivo) للمركبات :
3-(acetyl Salicyloyl)-5,6 –O-isopropylidene-L-ascorbic acid ,2,3- (acetyl Salicyloyl)-5,6 –O-isopropylidene-L-ascorbic acid and 2,3,5,6-Tetra(acetyl Salicyloyl)-L-ascorbic acid
وقياس تركيز الاسبرين المتحرر في مصل الدم بعد مرور (2,3,4,6,8,10) ساعات من اعطاء الحيوان الجرعة حيث اظهرت النتائج ان اعلى تركيز للاسبرين كان بعد اربع من اعطاء الحيوان الجرعة وهذا يتطابق مع المراجع العلمية .

In vivo study of compounds 3-(acetyl Salicyloyl)-5,6 –O-isopropylidene-L-ascorbic acid ,2,3- (acetyl Salicyloyl)-5,6 –O-isopropylidene-L-ascorbic acid and 2,3,5,6-Tetra(acetyl Salicyloyl)-L-ascorbic acid

F. T. Maher , A-J. Mukhlis,* A. I. Abuod , **N. A. Naji
Department of Chemistry, College of Education, Ibn Al-haithem ,University of Baghdad
***Ministry of Science and Technology**
**** Department of Chemistry College of Science – Tikrit University**

Abstract

In vivo study was made for the coumpounds 3-(ocetyl Salicyloyl)-5,6-O-isoprpy lidene-L-ascorbicocid,2,3-(acetyl Salicyloyl)-5,6-o- isopropylidene-L-ascorbic acid and 2,3,5,6-(acetyl Salicyloyl)-L- ascorbic acid .And a measurement was mod for the concentration of the liberated aspirin in blood samples a fter (2,3,4,6,8,10) hours of the initial dose for the animal .The results showed that the highest concentration of aspirin was after four hours of giving the dose to the animal which is in accordance with pharmacokinetics studies

Introduction

Aspirin, the salicylic ester of acetic acid, was introduced into medicine in 1899 and is used for its analgesic, antiinflammatory, antipyretic, and antithrombotic effects. Once in the body, it is hydrolyzed to salicylate, which is also active. The antiinflammatory and analgesic effects of aspirin are roughly equivalent to those of many NSAIDs. Aspirin is used in the treatment of many inflammatory and autoimmune conditions such as juvenile arthritis, rheumatoid arthritis, and osteoarthritis. Because of its antithrombotic effects, aspirin is useful in preventing or reducing the risk of myocardial infarction and recurring transient ischemic attacks (TIAs). Aspirin was officially approved by the FDA in 1939. During most of this century, it was mainly used for its antiinflammatory and analgesic properties. In the 1980s, its ability to inhibit platelet aggregation was realized and it became an important antithrombotic agent. More recently, it has been shown that long-term (e.g., >= 10 years) regular consumption of aspirin may lower the risk of developing colorectal cancer(1,2,3). It is now thought that aspirin may possess antiproliferative actions. A sustained-release aspirin (Asacard) was approved for use in the UK in February 1998; phase I studies on this product were initiated in the US also in February 1998(4)

Several interactions occur between acetazolamide and aspirin. Salicylates displace acetazolamide from plasma protein binding sites and also decrease acetazolamide renal excretion. Conversely, acetazolamide may increase the renal elimination of salicylates by increasing urinary pH. Aspirin can precipitate acetazolamide CNS toxicity, however, the effects of acetazolamide on aspirin may not be clinically significant.

The risk of bleeding is increased if aspirin is administered to patients already receiving anticoagulants. Aspirin can displace warfarin from protein-binding sites and can increase the risk of bleeding during heparin or warfarin therapy because of its effect on platelet aggregation. Aspirin-induced GI bleeding may be worse in anticoagulated patients. Also,

aspirin, in high-doses, has a hypoprothrombinemic effect. Aspirin and warfarin may be used together, however, if aspirin is administered before warfarin therapy is begun. Combination

therapy with both aspirin and warfarin has been shown to reduce mortality compared to warfarin therapy alone in patients with artificial heart valves. Aspirin can potentiate the anticoagulant effect of heparin; however, these two agents are often used together in the treatment of acute myocardial infarction. Regarding thrombolytic agents, while the risk of bleeding is increased if aspirin is coadministered, it is likely that a high percentage of patients who receive thrombolytic agents will be already receiving aspirin.(5,6)

In 1970, Linus Pauling wrote a book entitled "Vitamin C and the Common Cold" in which he suggested that megadoses of Vitamin C would aid in the prevention of colds. However, subsequent studies have shown that high intake of Vitamin C does not correspond to a lower rate of respiratory viral infections.Additionally, diets high in Vitamin C were found to be detrimental to a persons health. For example, ascorbic acid can react with iron ions to produce hydroxy radicals, which leads to cellular damage. In addition, a condition called withdrawal scurvy is associated with megadoses of Vitamin C(7,8). This condition is observed with a high ascorbic acid diet, when the body begins to excrete the excess vitamin C at a common rate. When the intake of vitamin C is decreased, the excretion rate from before continues at the same rate, eliminating the lower dosage amount at a high rate. Therefore, people begin to exhibit signs of scurvy due to this phenomenon. Another side effect from megadoses of Vitamin C is the formation of kidney stones from the buildup of oxalic acid and uric acid(9,10). A final negative side effect is the experiencing of diarrhea and skin rashes, if the megadoses are taken suddenly in large amounts without allowing the body to adjust to the high concentrations by taking slowly increasing amounts.

Experimental

Compounds 3-(acetyl Salicyloyl)-5,6 –O-isopropylidene-L-ascorbic acid (1) ,2,3-di(acetyl Salicyloyl)-5,6 –O-isopropylidene-L-ascorbic acid (2) and 2,3,5,6-Tetra(acetyl Salicyloyl)-L-ascorbic acid (3) were synthesis and identification according to the literature(11,12,13)

Three individuals of English Angora rabbits weighing (1.80,1.92,2.1) Kg were fasted for 48 hrs. prior to drug administration with free access to drinking water. Each single rabbit forced fed 1.5g of tested drug (3-(acetyl Salicyloyl)-5,6 –O-isopropylidene-L-ascorbic acid(1) ,2,3- (acetyl Salicyloyl)-5,6 –O-isopropylidene-L-ascorbic acid(2) and 2,3,5,6-(acetyl Salicyloyl)-L-ascorbic acid(3)); the drug introduced by a pice of cucumber contaminated with a tested dose. Blood samples were collected after and before the drug administration at different intervals of time (0,2,3,4,6,8,10 hr.) the blood was left at room temperature for about half an hour then the serum was separated by centrifuging for 15 minutes at 3500 rpm. and stored at -20^{o}C until analysis was performed . The concentration of aspirin was followed at fixed wave length at 277 nm(14) .

Result and Discussion

In this study 1.5 gm the compounds (1),(2),(3) were used (oral administration to a group of three rabbits).

Blood sample was taken from the rabbits then the serum was separated by centrifuge,150 μL from serum was diluted with methanol (25 ml) .The aspirin concentration was measured in serum at 277 nm .

-The aspirin concentration after (2 hr.) was ($3.71X10^{-5}$ M) , (3 hr.) was ($3.2X10^{-3}$ M) , (4 hr.) was ($4.08X10^{-3}$ M) , (6 hr.) was ($3.41X10^{-3}$) ,(8 hr.) was ($4.61X10^{-3}$ M) , (10 hr.) was ($3.601\ X10^{-5}$ M) for the compound (1) .

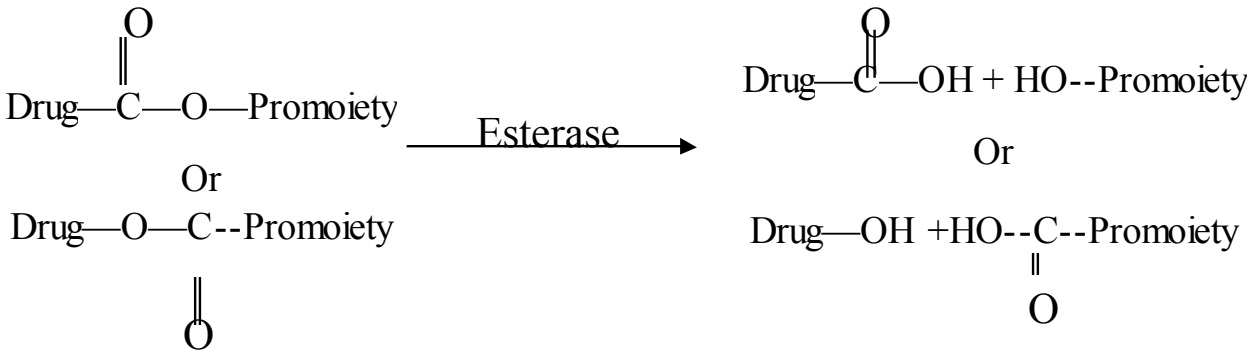
-The aspirin concentration after (2 hr.) was ($7.52X10^{-5}$ M) , (3 hr.) was ($6.40X10^{-3}$ M) , (4 hr.) was ($8.38X10^{-3}$ M) , (6 hr.) was ($6.68X10^{-3}$ M) ,(8 hr.) was ($9.18X10^{-4}$ M) , (10 hr.) was ($7.25X10^{-5}$ M) for the compound (2) .

-The aspirin concentration after (2 hr.) was ($1.47X10^{-4}$ M) , (3 hr.) was ($1.27X10^{-2}$ M) , (4 hr.) was ($1.68X10^{-2}$ M) , (6 hr.) was ($1.34X10^{-2}$ M) ,(8 hr.) was ($1.84X10^{-3}$ M) , (10 hr.) was ($1.46X10^{-4}$ M) for the compound (3) .Table (1-3) ,Figure (1-3)

The results show that the concentration of aspirin was low in the first hour and then increased with time increased until 4 hours (the maximum concentration of aspirin) .

After 4 hour (6,8,10 hr.) the concentration of aspirin was decreased .After 10 hours the concentration of aspirin was equal to the aspirin concentration in (2 hours).

Hydrolysis normally accomplished by esterase enzyme present in serum and other tissues capable or hydrolyzing a wide variety of ester linkages like (Ester hydrolase, Lipase ,Cholesterol esterase , Acetyl cholinesterase ,Carboxypeptidase) (15).



The ester moiety is subsequently hydrolyzed in the gastrointestinal tract and the agent is absorbed as aspirin and vitamin C.

Schnabelruch and coworker(16) (1990) refer to the hydrolytic release of the bioactive agent (carboxymethyl cellulose-2,2-dichloropropionates) (CMC ester) is mainly dependent on the hydrophilicity of the CMC ester . In the case of containing enzymatic cleavable the release can be accelerated by addition of esterase .The release of 2,2-dichloropropanic acid from CMC ester at 30^0C and pH 7 without addition of esterase was 8 % after 100 hours while The release of 2,2-dichloropropanic acid from CMC ester at 30^0C and pH 7 with addition of esterase was 50 % after 100 hours.

Yi-Nuo Pang et al (2002) (17) refers to that the recovery of dexamethasone (%) in colon after (1,3,4,5,6,7,9) hours (oral administration) was (0,0,20.5,18.0,10.2,15.2,18.2)% respectively. These results showed that the ester type prodrugs of dexamethasone/dextran (DSD) release dexamethasone preferentially on colonic contents after the hydrolysis of dextran to small oligosaccharides.The dextran conjugate survives the passage through upper GI tract although the high level of esterase in small intestine, indicating that dextran protects ester bond from hydrolysis by esterase. This result, together with the observation mentioned above, suggests that bacterial enzymes in the colon are responsible for hydrolysis of dextran conjugates. When DSD reached the colon, dextran was completely hydrolyzed into smaller oligosaccharides and exposed the ester bonds to esterase, which led to the rapid release of dexamethasone.

The bacterial count in the colon is much higher than that in upper GI tract(18). The colonic micro flora produces a variety of enzymes, including azoreductase, various glycosidases and amidases, which are not present in the stomach or the small intestine. Therefore, enzyme dependent drug release, which relies on the existence of enzyme-

producing microorganisms in the colon, could be used to deliver drug to the colon after enzymatic cleavage of degradable carrier bonds.

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Table (1) Concentration of aspirin in rabbit blood serum [compound (1)]

Time (hr)	Concentration M
0	0
2	$3.71X10^{-5}$

3	$3.2X10^{-3}$
4	$4.08X10^{-3}$
6	$3.41X10^{-3}$
8	$4.61X10^{-4}$
10	$3.601X10^{-5}$

Table (2) Concentration of aspirin in rabbit blood serum [compound (2)]

Time (hr)	Concentration M
0	0
2	$7.52X10^{-5}$
3	$6.40X10^{-3}$
4	$8.34X10^{-3}$
6	$6.68X10^{-3}$
8	$9.18X10^{-4}$
10	$7.25X10^{-5}$

Table (3) Concentration of aspirin in rabbit blood serum [compound (3)]

Time (hr)	Concentration M
0	0
2	$1.47X10^{-4}$
3	$1.27X10^{-2}$
4	$1.68X10^{-2}$
6	$1.34X10^{-2}$
8	$1.84X10^{-3}$
10	$1.46X10^{-4}$

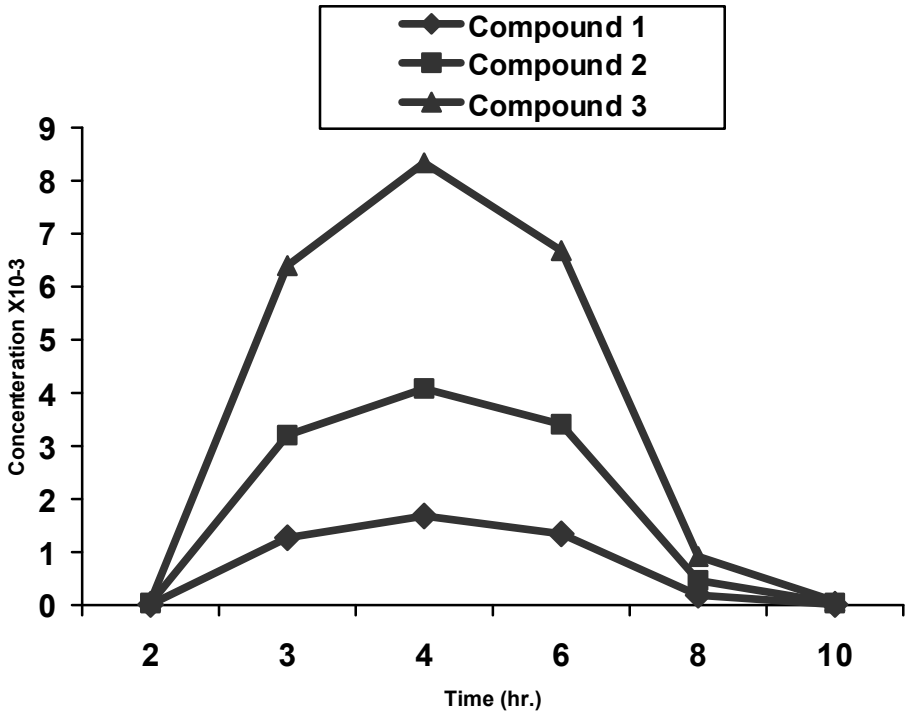

Fig. (1): concentration of aspirin released