Thiopurinol appeared to have no immediate effect on pyrimidine metabolism as judged by levels of orotic acid excretion in man or in the pig. *In vitro* studies showed that no major metabolites of thiopurinol were found in intact human or pig erythrocytes.

Discussion

DR. S. KRANE (*Boston and Oxford*) There is some evidence that allopurinol, and undoubtedly thiopurinol, has an action of turning off *de novo* purine synthesis by binding PRPP. They have now shown that PRPP levels determine the activity of the aggregate of PRPP amino-transferase and that the lowering of PRPP levels by a drug such as allopurinol or thiopurinol would then decrease the activity of the dispersed enzymes. So it is not the nucleotide that regulates the biosynthesis but the level of PRPP, not only acting as substrate, but by determining the total activity of the enzymes. That would make more sense, since in the patient with PRPP deficiency it would also not reduce the level of PRPP at this site of synthesis.

DR. SIMMONDS We don't agree because we feel it is the availability of the PRPP in the body that is important. We have found enormous formation of allopurinol which must require a tremendous amount of phosphate of one form or another to form it and we have not been able to measure the PRPP levels as these are too low to detect any difference. In the cases of orotic aciduria where there must also be a tremendous availability of PRPP you do not find gout or overproduction of purine. There are anomalies which I think require investigation before you can stand up and say this is the effect.

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Withdrawal of Allopurinol in Patients with Gout. By W. Y. LOEBL and J. T. SCOTT (*Charing Cross Hospital and Kennedy Institute of Rheumatology, London*) Published in full in the *Annals* 1974, 33, 304.

Kinetics of Salicylate Metabolism. By T. GIBSON, G. ZAPHIROPOULOS, J. GROVE, B. WIDDOP, and D. BERRY (*Department of Rheumatology and Poisons Unit, Guy's Hospital, London*)

The major metabolites of aspirin, salicylic acid (SU), and salicyl phenolic glucuronide (SPG) are rate limited in their formation (Levy and Tsuchiya, 1972). With increasing doses of aspirin their synthesis and excretion approach a zero order process (i.e. unlike the metabolic products of most drugs which are formed by a first order process, their rate of biosynthesis does not increase in direct proportion to the dose of drug and will not increase further when a critical ceiling dose is exceeded. This is presumably due to enzyme-substrate saturation).

The reported variable plasma salicylate levels achieved in different subjects given the same dose of aspirin have a number of known causes (Cummings and Martin, 1964). Added to these may be an individual variation in the

capacity for producing and excreting the major metabolites, particularly salicylic acid (Paulus, Siegal, Mongan, Okun, and Calabro, 1971).

To examine this hypothesis 9 subjects with active rheumatoid arthritis or painful spinal disorders were given 65 mg/kg body weight aspirin daily in divided doses for 5 days. Plasma salicylate levels were estimated 2 hours after each midday dose. Urine was collected continuously for estimation of salicylic acid, salicyl phenolic glucuronide and salicylic acid.

In 4 subjects the study was extended to 11 days with the dose of aspirin increased to 100 mg/kg for the last 3 days.

Plasma salicylate levels rose to a peak on the third or fourth day then levelled. There were individual differences in the plasma salicylate levels on day 3 or 4 (mean 19.9 mg/100 ml, range 13.3 mg–28.5 mg/100 ml). The differences could not be related to individual variations in SU excretion with this dose regimen and there was no difference between the mean levels of those with rheumatoid arthritis and those with noninflammatory backache.

Increasing the dose of aspirin to 100 mg/kg in 4 patients induced an expected rise in plasma salicylate levels reaching a mean value of 34.5 mg/100 ml (range 29.5–45.5 mg/100 ml) on day 11. An increase was also seen in the urine SU of all subjects, but this was of a small order and was least in the subject who had the highest plasma salicylate level. 3 of the 4 patients also showed some increase of SPG excretion but no increase occurred in the patient with the highest plasma salicylate level.

The proportion of SU and SPG in the urine declined during the period of increased dosage and there was a marked increase in the proportion of salicylic acid (SA).

Conclusion

In 9 subjects given 65 mg/kg bodyweight aspirin it was not possible to show any association between plasma salicylate levels and individual variations in salicylic acid excretion.

When the dosage was increased to 100 mg/kg in 4 subjects a capacity for increasing SU excretion was shown, but this was least in a patient who had the highest plasma salicylate level. In the same patient the capacity for SPG formation was apparently exceeded by the higher dose and it is possible that the more limited capacity for SU and SPG formation in this case was responsible for the comparatively high plasma salicylate level.

At the higher dose of aspirin the proportion of SU and SPG in the urine declined in all 4 subjects reflecting the decreasing capacity for their formation. A compensatory increase in unchanged salicylic acid excretion was seen and this assumes a more important excretory role with increasing dose of aspirin.

Discussion

DR. W. C. DICK (*Glasgow*) Firstly, in view of the recent reports of possible hepatotoxicity of aspirin, did you take the opportunity of measuring liver enzymes after treatment as well as before? Secondly, did you relate your findings in any way to the albumin concentration; and finally, I would take issue with the word significant. I think the numbers are too small and the range too large for you to use the word significant in a statistical sense. There is certainly insufficient data to be certain of a lack of difference between rheumatoids and patients with backache.

DR. ZAPHIROPOULOS The answer to the first question is no, we did not repeat them. We did measure the albumin level of all patients, both rheumatoid and nonrheumatoid, and they were very comparable. This is a criticism of the previous paper by Paulus and others where their patients with rheumatoid arthritis had lower levels of albumin and one was frankly hypoalbuminaemic. We thought that this may well have accounted for their findings of a wide range of plasma salicylate levels because these patients tended to have the lower plasma salicylate levels. We agree the number of patients was very small. Significance was not a point we were trying to make. We just had to compare two groups of patients, one with inflammatory and one with noninflammatory disease, and it just happened that the level of salicylates achieved on day 3 or 4 was very comparable.

DR. A. ST. J. DIXON (Bath) Should not conclusions with regard to aspirin toxicity be based on aspirin blood levels as well as salicylate blood levels? It is the aspirin which has not been hydrolysed by esterase which is responsible for a lot of the toxicity.

DR. ZAPHIROPOULOS This may be a point.

DR. D. I. HASLOCK (Middlesbrough) Did you just measure bulk salicylate levels or did you differentiate free and bound salicylate? Secondly there is recent evidence (Menguy, Desbaillets, Masters, and Okabe, 1972) of sex differences in salicylate metabolism. I wonder if any of your differences are explicable on the basis of patients's sex.

DR. ZAPHIROPOULOS We did not look at the differences on the basis of sex, the numbers were too small. We did not differentiate between bound and unbound plasma salicylates.

DR. A. G. MOWAT (Oxford) I wonder if I might come back to your albumin levels. You criticize Paulus because the values were lower in the rheumatoids but you can, of course, correlate the serum albumin value with the activity of the disease and so it may well be that if you got normal albumins you had relatively inactive rheumatoids.

DR. ZAPHIROPOULOS Yes, this is a fair point, except that four cases included in this study had, on clinical criteria, active rheumatoid arthritis. They had a normal range of plasma albumins, the lowest value being 3.4 g/100 ml. Paulus included patients who had albumins below 3.0 g/100 ml. This might have accounted for the wide variation of plasma salicylate levels noted in his patients. One must also take into account urine pH. This was a parameter not mentioned in Paulus's study. We tried to monitor urine pH continuously during the study and it did not vary a great deal. It was between 5.2 and 6.4 and we do know that renal clearance of free salicylate is sensitive to urine pH; it increases more than tenfold when urine pH changes from below 6.0 to above 7.0.

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Joint Involvement in Spondylo-epiphyseal Dysplasias. By M. F. KAHN, M. T. CORVOL, and S. DE SÈZE (*Centre Viggo Petersen, UER Lariboisière-Saint-Louis Université de Paris*)

Early osteoarthritis has been described as a usual feature of multiple (spondylo) epiphyseal dysplasias (MED). A reappraisal of the joint involvement in MED has been conducted on 30 cases seen in 10 years at Le Centre Viggo Petersen. For this study we concluded that the joint involvement in MED, when seen in early stages, should not be described just as osteoarthritis. Clinically, 6 of these cases presented as recurrent inflammatory polyarthropathies, superficially resembling rheumatoid arthritis, but with neither biological nor anatomical changes. 22 cases had several loose bodies in different joints associated with osteochondritis and geodic lesions of subchondral bones without cartilage narrowing or bone destruction. In 6 cases, a very peculiar vertebral disc lesion leading to vertebral fusion was seen.

Osteoarthritis, when present (18 cases), appeared to be secondary to the previous lesions, just as in metabolic arthropathies and Kaschin-Beck disease. We think that osteochondrodysplastic arthropathy deserves an autonomous description.

Discussion

DR. W. H. DE HAAS (Amsterdam) May I please show a few slides? This is a patient suffering from metaphyseal dysostosis, which of course is not quite the same as epiphyseal dysostosis. He is clearly dwarfed and his height is 4 foot. I would like to show you some x-rays of his bones and joints, comparing x-rays at age 10 and 44 years. On the left hand aged 10, and you will see that this has nearly completely normalized in the hand at age 44. The same goes for the feet, especially the calcaneal bones. This is the knee which shows a wild structure at age 10 and which has become nearly normal at age 44. The pelvis, which shows chaotic lesions which have cleared up on the next slide. So in patients suffering from these diseases one should not be too panicky and wait for some time, for bone may normalize completely and joint function be impaired only slightly.

PROF. E. G. BYWATERS (Taplow) With our interest in children I would like to enquire what were the radiological changes in the child Dr. Kahn showed at the age of 4 and the age of 10. What sort of radiological appearance would be seen to differentiate this syndrome in the young from juvenile rheumatoid arthritis?

DR. KAHN If you consider the peripheral lesions, it is quite simple at the early stages. In epiphyseal dysplasias, the deformations and the subchondral bone lesions are present whereas no cartilage narrowing can be seen. The problem is much more difficult in long duration patients. In the literature, I think that some patients reported as epiphyseal dysplasia were in fact juvenile rheumatoid arthritis, but even in the most difficult cases you may have the answer if you analyse the less afflicted joint, where the lesions are still typical. Of course, you get the answer easily if the vertebral lesions are present. No such radiological appearances can be found in juvenile rheumatoid arthritis.