THE HYPERSENSITIVITY REACTIONS TO PARA-AMINOSALICYLIC ACID (P.A.S.)

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Para-aminosalicylic acid (P.A.S.) was first used in 1946 for the treatment of tuberculosis by Lehmann (1946). With the exception of nausea and vomiting, which Lehmann himself described, it was at that time thought that the drug was free from side-effects. However, with its increasing use, reports of other toxic reactions began to appear (Nagley and Logg, 1949: Hemming and Stewart, 1949) and there now exists an extensive literature on the subject.

These reactions fall into three groups (Dixon, 1954). First is a natural intolerance to the drug which as many as 58% of patients (Medical Research Council, 1950) experience, whose manifestations (nausea, vomiting and sometimes diarrhoea) appear very soon after starting the treatment.

Secondly, pharmacological side-effects have been described. These consist of hypoprothrombinaemia (Swanson, 1949), hypokalaemia (Cayley, 1950), hypothyroidism (Komrower, 1951) and hyperthyroidism (Tandhanand and Buri, 1956). The alterations in thyroid metabolism are usually associated with the occurrence of a goitre.

Thirdly, there are the hypersensitivity reactions, and these are usually the most serious. Table 1 lists these reactions.

Kniest (1952) has reported an anaphylactic reaction immediately after restarting treatment in two cases that had already shown some allergy to P.A.S., but this should be regarded as an exaggerated version of the normal hypersensitivity reaction.

The present case is reported because it shows so many of the hypersensitivity reactions to P.A.S., and helps to shed some further light on them. In addition, ascites and pleural effusion have not previously been reported as complications of P.A.S. therapy. Furthermore it is the first report of P.A.S. sensitivity following the administration of calcium B-P.A.S.

<table>
<thead>
<tr>
<th>Fever</th>
<th>Cutburt (1950)</th>
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<tr>
<td>Skin rash</td>
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<td>Blood dyscrasias</td>
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<td>Dixon (1954)</td>
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<td>(b) Glandular fever cells</td>
<td>Cannemeyer et al. (1955)</td>
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<td>Muri (1952)</td>
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<tr>
<td>Vasomotor rhinitis</td>
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<td>Löeffler's syndrome</td>
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<td>Pleural effusion</td>
<td>Present case</td>
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<td>Ascites</td>
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Calcium 4-Benzamidosalicylate (Calcium B-P.A.S. 'Therapas')

In an attempt to overcome the high degree of intolerance found when P.A.S. is administered as the normal sodium or calcium salt (in solution, in cachets or in granules), Bavin and James (1953) described this new substance which is insoluble and, perhaps for that reason, tasteless. It is broken down in the body to liberate P.A.S. and benzoic acid. Preliminary reports suggest that calcium B-P.A.S. is therapeutically as effective as the normal salts of P.A.S., and produces intestinal disturbances in a far smaller proportion of cases.

Case Report

The patient, a girl of 7 years, developed primary tuberculosis and was treated with I.N.H. and calcium B-P.A.S. There was nothing relevant in either her previous medical history or in her family history. Her
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elder brother (the only sibling) and both her parents were well and showed no evidence of active tuberculous infection; the contact was never found.

For convenience all dates have been related to the day she first received P.A.S. ("P" day, April 24). Fig. 1 illustrates the progress of the case.

31.3.56 The patient was seen with a rash on her shins (P − 24) which resembled erythema nodosum.
2.4.56 Tuberculin jelly test positive, control negative.
4.4.56 Radiological report (1).
5.4.56 Erythema nodosum settling slowly. A fairly constant evening pyrexia of 99° F. noted.
20.4.56 Radiological report (2)
(3) (P − 4) Pathological report (2)
20.4.56 (P day)
23.5.56 A rubella-like eruption appeared during the afternoon but lasted only two hours. Its significance was not appreciated.
12.5.56 The eruption recurred, and with it the temperature rose to 101° F. The cervical nodes, especially those in the posterior triangles, were enlarged.
21.5.56 For the first time nausea was experienced on taking the B-P.A.S. The dose was reduced with no improvement.
17.5.56 The child's condition was much worse, and she looked ill. An irritating morbilliform rash had replaced the rubella-like one and covered the whole body. The conjunctivae were suffused and her eyes were watering. Several small ulcers were present on the buccal mucosa and inside the mouth. The adenitis had increased considerably; not only were all the nodes in the neck enlarged, but also those in the axillae and groin, though the spleen could not be felt (nor could it at any other time). All antituberculosis therapy was stopped on this day.

The eyelids and face were swollen and the ankles slightly oedematous. She was complaining of quite severe abdominal pain and on examination the liver edge was palpable and tender. The urine showed the presence of bile salts and pigments, and there was albumin + + (bed-side analysis).

Liver edge palpable three fingerbreadths below the costal margin. Temperature 101-104° F. Pathological report (3)

The temperature returned to normal, but the liver was now palpable five fingerbreadths and jaundice could be detected, though it was not at any time very marked.

Subjectively the child felt much better but on examination signs were detected in the chest for the first time. The percussion note was

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Fig. 1.
dull in the right axilla and air entry was diminished over the right lower lobe.

29.5.56 Radiological report (3)
(P+35) Pathological report (4)
30.5.56 Ascites was found. The skin was beginning
to peel over both thumbs and thenar eminences as the rash was starting to fade.
2.6.56 General condition much improved. Liver
dge decreased to two fingerbreadths. Ascites
was now no longer detectable. The oedema
had subsided. Pulmonary signs were un-
altered. The exfoliation was spreading all
over the body.

4.6.56 The chest was clinically clear. The oral and
conjunctival ulcers had settled. The adenitis
was subsiding.

5.6.56 Radiological report (4)
(P+42) Pathological report (5)
12.6.56 All the signs had disappeared except for the
remains of the exfoliative process on the legs.
29.6.56 Child clinically very well. Appetite good.
(P+66) Up half day.
Radiological report (5)
Pathological report (6)

14.8.56 Gaining weight. Full activity.
(P+112) Radiological report (6)
Pathological report (7)
11.10.56 Radiological report (7)
(P+140) Pathological report (8)
1.10.56 Permitted to return to school.
(P+161)
10.9.57 The child is clinically very well. The primary
tuberculosis complex is no longer visible radi-
ologically.

Radiological Reports

(1) 4.4.56 Lung fields clear. Left hilum a little
suspicous.
(2) 20.4.56 The left hilar glands are enlarged and
there is some consolidation in the apical segment of the
lower lobe or in the posterior segment of the upper lobe.
The radiological appearances are consistent with
the presence of a primary tuberculous complex.
(3) 29.5.56 There is now a small effusion at the right
base and some fluid is also present in the intralobar
fissure. There may be a little afebrile atelectasis above it (Fig. 2).
(4) 5.6.56 The right lung field is now clear and there
is no evidence of fluid. The left hilar mass is unchanged
(Fig. 3).
(5) 29.6.56 The position of the left hilum has not
altered materially.
(6) 14.8.56 Comparison with the previous films shows
little change. The left hilar glands are still enlarged.
(7) 11.9.56 The enlarged glands at the left hilum
have not altered materially in size in the last month.

Pathological Reports

(1) 4.4.56 Hb 11-2 g. %. W.B.C. 7,600 per c.mm.
(5,800 polymorphs, 1,700 lymphocytes, 100 monocytes).
E.S.R. 42 mm./hr.
(2) 20.4.56 Hb 12-8 g. %. W.B.C. 13,000 per c.mm.
(8,400 polymorphs, 3,900 lymphocytes, 700 monocytes).
E.S.R. 41 mm./hr.
(3) 23.5.56 Hb 12-3 g. %. W.B.C. 9,000 per c.mm.
(3,500 neutrophils, 500 eosinophils, 5,000 lymphocytes).
A few of the mononuclear cells were atypical and
resembled those seen in glandular fever.
(4) 29.5.56 Urine: amber yellow. S.G. 1-016,
ph 7-0, albumin nil, bile salts nil, glucose nil, bile
pigments +, urobilinogen 1-5 units %, 6 leucocytes
and less than 1 R.B.C. per c.mm.
(5) 5.6.56 Hb 12-7 g. %. W.B.C. 13,000 per c.mm.
(7,600 polymorphs, 6,300 lymphocytes, 600 monocytes).
E.S.R. 24 mm./hr. Urine: bile salts +, bile pigments
++, urobilinogen 1-1 units %. A few of the mono-
cytes were atypical. Paul-Bunnell test was positive
to 1:16 only, i.e., negative.
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Stomatitis and conjunctival suffusion together with a puffy face and generalized oedema are typical of a drug fever, and albuminuria is often found in the same condition. The rash, too, which resembled erythema multiforme, can occur with a drug fever, and, as mentioned above, it also often accompanies the hepatitis and ‘glandular fever reaction’ following P.A.S.

Allergic reactions to P.A.S. therapy are not common in children (Todd, 1953) though they do suffer the same natural intolerance to the drug. Hepatitis does not appear to have been reported previously in a child though Oppe (personal communication) had a case which ended fatally. Both of Kniest’s (1952) cases of anaphylactic reaction were in children, the older of whom (aged 12) died from a concomitant flare-up of a tuberculous infection.

Summary

A case is reported of a child treated with P.A.S. who developed hypersensitivity reactions. These reactions included drug fever, lymphadenopathy with ‘glandular fever cells’ in the blood, hepatitis with jaundice and dermatitis with exfoliation. In addition the child developed Löffler’s syndrome with a pleural effusion and had ascites.

I wish to thank Drs. J. Fielding and P. L. Masters for the pathological reports and Drs. T. R. Riley and J. J. Stevenson for the radiological reports.

Considerable advice was received from the St. Mary’s Hospital Home Care Department, though, because the patient lived outside the area they cover, she did not come into their scheme. I would like to thank Dr. Lightwood and his team for all their assistance, and in particular I wish to thank Dr. Lightwood for his help in the preparation of this paper. I would also like to thank Dr. B. Kustow, whose patient the child is, for his permission to look after the child, and for his encouragement.

REFERENCES


Medical Research Council (1950). Ibid., 2, 1073.
Oppe, T. Personal Communication.