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Institute of Rheumatology, University of Siena, 53100 Siena, Italy
NICOLA GIORDANO, MD, assistant professor
ANTONELLA FIORAVANTI, MD, assistant professor
SIMONETTA SANCASCIANI, MD, assistant professor
ROBERTO MARCOLONGO, MD, professor

Medical Department, Ciba-Geigy, Origgio, Varese, Italy
CRISTINA BORGHI, PHD, associate professor, Postgraduate School of Toxicology, University of Milan

Correspondence to: Professor R Marcolongo.

Thrombocytopenia induced by nalidixic acid

Over the years the Netherlands Centre for Monitoring of Adverse Reactions to Drugs has received six case reports on patients with profound but transient thrombocytopenia probably induced by nalidixic acid (Negram, Mictral). The table gives the details of these patients.

Cases

Characteristically thrombocytopenia developed within 10 to 15 days of treatment with nalidixic acid, 4 g daily, and rapidly recovered after stopping the drug (table). All patients had platelet counts below 30×10^9/l and serious impairment of blood coagulation, haemorrhagic symptoms being recorded in five. In one case immediate relapse of thrombocytopenia on rechallenge with a single dose of 1 g nalidixic acid provided the proof for a causal relation. One patient concomitantly had a generalised rash. The bone marrow was studied in two patients and showed active megakaryopoiesis.

Comment

Case observations on patients with thrombocytopenia induced by nalidixic acid do not appear to have been described. The rare occurrence of thrombocytopenia is, however, briefly mentioned in the data sheet on Negram (in the Netherlands, but not in Britain) and in the sixth edition of *The Pharmacological Basis of Therapeutics*.[1] According to a report from the Australian Drug Evaluation Committee three cases of thrombocytopenia suspected to be induced by nalidixic acid were reported there during 1964-71.[2] The Committee on the Safety of Medicines has been notified of eight similar cases (J C P Weber, personal communication, 1984).

Apart from the positive result on rechallenge in one patient, several observations suggest a causal relation with nalidixic acid—in particular the rapid and complete recovery when the drug was discontinued. In two patients underlying disturbances of haematopoieses were excluded by examination of bone marrow. Urinary tract infections are not known to be associated with thrombocytopenia. No other suspected drugs than nalidixic acid were known to have been used. Although no specific tests were done, the induction time of 10 to 15 days, the rapid recovery, the active bone marrow, and the concomitant rash in one patient are consistent with an allergic reaction resulting in peripheral destruction of platelets. Nalidixic acid is excreted mainly by the kidneys, and it may be relevant that five of these patients were over 65 and that two of them had clearly impaired renal function.

It is concluded that the use of nalidixic acid is associated with the risk of developing sudden and severe thrombocytopenia. Although this reaction seems to be rare, there may have been considerable underreporting. The notification of similar occurrences to national drug authorities is recommended.

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Netherlands Centre for Monitoring of Adverse Reactions to Drugs, Ministry of Welfare, Public Health and Culture, PO Box 439, Leidschendam, The Netherlands
R H B MEYBOOM, MD, head

Early onset scoliosis: a call for awareness

School screening programmes, carried out routinely in the United States and established in a few centres in the United Kingdom,[2] have identified many children with spinal deformities. These deformities, however, are generally mild curves, and controversy exists about the need for their detection. A report by the British Orthopaedic Association and the British Scoliosis Society concluded that more data are required before school screening throughout the United Kingdom can be recommended.[3] If school screening is to be adopted children at special risk need to be identified. I therefore reviewed all patients with infantile idiopathic scoliosis or congenital scoliosis who had attended a regional scoliosis service to see whether diagnosis had been delayed and the appropriate advice or treatment offered.

Patients, methods, and results

I reviewed the case records and radiographs of 139 patients seen during 1976-83. Thirty nine had progressive infantile idiopathic curves and 100 congenital curves, representing 8% and 21% respectively of all new referrals. Ages at diagnosis, at referral for specialist advice, and at referral to the scoliosis clinic were recorded. The circumstances of diagnosis and subsequent management were noted. The severity of curvature was measured from the first available radiograph and from radiographs taken at the initial visit to the scoliosis clinic.

The table shows the results. In both groups a delay of over five years occurred between initial diagnosis and referral to the scoliosis service. Accepting that informed advice is needed when a curve is 40° or more in a child aged over 2, then in 21 children with idiopathic curves the delay was excessive. In 16 of these the diagnosis was made by a parent, in three by a

Details of patients with reactions to nalidixic acid

Case No	Age and sex	Daily dose of nalidixic acid (g)	Other drugs	Platelet count ($\times 10^9$/l)	Complications	Time relation*		Other factors
						Interval	Course	
1	53 F	4	Sodium bicarbonate	16	Petechiae, epistaxis, vaginal bleeding	10 days	5 days	Impaired renal function, serum creatinine 370 μmol/l (4·2 mg/100 ml)
2	91 M	4		6	Bleeding time over 15 minutes	14 days	5 days	Renal insufficiency, serum creatinine 625 μmol/l (7·1 mg/100 ml), rash
3	75 F	4	Digoxin	27	Petechiae	15 days	About 6 days	Treated with prednisolone; sternum puncture: active megakaryopoiesis
4	66 F	4		7	Ecchymosis	3 days	1 week	Relapse of thrombocytopenia 32×10^9/l on rechallenge with 1 g nalidixic acid
5	73 F	4	Insulin	9	Purpura	12 days	5 days	
6	81 F	4		6	Ecchymosis	12 days	4 days	Sternum puncture: active megakaryopoiesis, increased number of plasma cells. After recovery: normal bone marrow

*Interval = interval between starting nalidixic acid and development or discovery of thrombocytopenia. Course = interval between stopping nalidixic acid and recovery of thrombocytopenia.

paediatrician, and in two by an orthopaedic surgeon. In every case in which the parents noted the deformity immediate advice was sought and, with one exception, the family doctor referred the child to hospital. Of six children seen by a paediatrician, only one was referred quickly to an orthopaedic surgeon. Four became severely deformed as a result of delay. Fifteen children were under the care of orthopaedic surgeons. Three received ineffective treatment and four, not offered any treatment, had the progression of their curve carefully recorded.

In the group with congenital curves 50 children, aged 2 or over, had curves of more than 40° when seen at the scoliosis clinic. Delay in diagnosis had occurred in 11, in seven of whom the deformity had gone unnoticed when the child had been previously examined by a paediatrician or an orthopaedic surgeon. In the remaining 39 the mean age had risen from 2·2 to 11·4 years between diagnosis and referral to the scoliosis clinic. The deformity had been observed initially by a parent in 24 children, a paediatrician in eight, an orthopaedic surgeon in four, and community doctors in three. In only five cases did parents delay seeking advice. Paediatricians delayed in four out of 10 children. Orthopaedic surgeons waited on average 8·6 years before referring to a specialist centre, by which time the mean curve was 73°. Of 32 children under the care of orthopaedic surgeons, 18 had no treatment, 13 were treated by exercises or a brace, and one underwent spinal fusion.

Ages at diagnosis and referral and severity of deformity in 139 patients with early onset scoliosis

Deformity	Mean age at diagnosis (years)	Mean age at referral (years)	Mean deformity at referral (degrees)
Infantile idiopathic	1·2	6·8	57
Congenital	4·4	9·5	48

Comment

This study suggests that the problem in early onset scoliosis is what happens after diagnosis. Similar trends have been observed in data submitted from other areas to the British Scoliosis Society's study group on screening and natural history. During 1983 the mean age of patients referred to the Leeds scoliosis centre with infantile idiopathic curves was 7·2 years and with congenital curves 12·2 years. The mean deformity in these groups was 63° and 55° respectively (R A Dickson, personal communication). Education of paediatricians and orthopaedic surgeons would be the single most effective method of ensuring that young children with spinal deformity are referred in good time to the nearest scoliosis service.

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Royal Hospital for Sick Children, Glasgow G3 8SJ
A N CONNER, MB, FRCS, consultant orthopaedic surgeon

Surgical inpatients who do not "occupy" hospital beds

Inpatient workload is often based on Hospital Activity Analysis using data from the originating document HMR1(IP). Although it is well recognised that information gained from this source often underestimates work actually done,[1 2] decisions on allocation of both financial and physical resources depend on it.[2] This study was stimulated by an analysis of data collected prospectively for internal unit research which disclosed several inpatients who had been "discharged" on the same day as their admission.

Present study and results

Data on all patients admitted in 1983 to one surgical unit of a district general hospital were collected prospectively on printed questionnaires and computerised. Details of inpatient treatment, materials, and services used and duration of hospital stay were included. The computer was programmed to identify those patients whose admission dates were the same as their discharge dates, and the data on the 53 patients so identified were studied in greater detail. The series did not include patients admitted for day case procedures or those referred for surgical opinion from the accident and emergency department, who were discharged without admission. Hospital Activity Analysis printouts were requested for our unit for 1983, and these were searched to see if the 53 patients were there.

The patients comprised 21 men and 32 women aged 19-88 years (mean 48·5). The table gives the reasons for their discharge and the numbers of hours that they had spent in hospital. It also lists the numbers of patients missing from the printouts.

All 17 patients who died or were transferred to another hospital had been looked after by the surgical team for most of the time that they had been in our hospital. Every patient transferred had been accompanied by an anaesthetist proficient in resuscitative procedures. Six patients were admitted to the intensive care unit and four received assisted ventilation shortly after arriving in hospital. All patients were "clerked" by the house surgeon and put in clean beds and given full nursing care appropriate to their condition. Thirty of these patients had at least one blood test and 48 had at least one *x* ray examination. Five patients had operations lasting a total of 16 hours, and 24 units of blood were used.

Comment

Use of hospital inpatient resources is currently calculated for each "full" day a patient spends in the ward.[3] In practice a patient is deemed to have occupied a bed for one full day if he is present in the bed before and after midnight.[4] Hence inpatients who do not occupy beds for a full day as defined will not be considered to have used resources. Allowance is made, however, for day case patients who are admitted and discharged the same day.

Although the patients in this study were relatively few, their identification was important for three reasons. Firstly, they made a larger demand on manpower and resources than official estimates suggested. Secondly, more than half of the patients were not included in Hospital Activity Analysis and their capacity to use resources was further underestimated. Thirdly, some of the patients were in a high risk category, so that while they were being attended to the needs of other patients were apt to have been inadequately met.

The Department of Health and Social Security has done research into specialty costing and has shown that the amount of money spent by a unit can be calculated fairly accurately.[3] But the methods used have not been widely implemented, and it will therefore be some time before the present anomaly in the estimation of expenditure is eliminated.

I thank Mr John Lynn for permission to study his patients and the regional statistician for the printouts.

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Department of Surgery, Ealing Hospital, Southall, Middlesex UB1 3HW
DAVID P SELLU, CHM, FRCS, registrar

Details of 53 patients who went home or died on the same day that they were admitted

Reason for "disposal"	No	Mean duration of stay in hospital (hours)	No not included in Hospital Activity Analysis returns	Comment
Deaths	9	8	4	Two patients had leaking aortic aneurysm, one severe head injury
Transfers	8	5	5	Three patients had severe head injuries, two aortic aneurysms
Self discharges	21	13	12	Seven patients had head injuries, six abdominal pain
Reason for admission no longer present	6	6	4	Examples included disappearance of breast lumps, emergency condition better after initial observation
Others	9	4	6	Examples included admission while surgical registrar busy in theatre, later discharged