Adverse drug reactions of the month

Tiaprofenic acid and severe cystitis

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Tiaprofenic acid is a nonsteroidal anti-inflammatory drug, which has been marketed in the UK since 1982 as Surgam. Since 1989, the Data Sheet/Summary of Product Characteristics has mentioned bladder irritation and urinary tract disorders. After the first report linking tiaprofenic acid with interstitial cystitis was published in 1991,¹ there were several published reports referring to its potential severity.²⁻⁸ Changes to the product information were instituted in July 1994: these warned about cystitis and the need to withdraw the drug immediately if urinary symptoms develop. The drug was contraindicated in patients with a history of recurrent cystitis, micturition disorders, or prostatism.⁹ Advice was sent to all doctors and pharmacists in the UK in August 1994 through an article in *Current Problems in Pharmacovigilance*.¹⁰ The present paper reviews how the patterns of reporting of cystitis associated with tiaprofenic acid in the UK have changed with time.

Methods

The Committee on Safety of Medicines/Medicines Control Agency (CSM/MCA) receive reports of suspected adverse drug reactions (ADRs) from many sources, including Yellow Cards from UK doctors and pharmacists. These reports are electronically scanned onto the ADROIT (Adverse Drug Reactions Online Information Tracking) database. This database was interrogated and UK cases with lower urinary tract symptoms or cystitis were retrieved. The year that each ADR was reported, the date of onset of the reaction and its nature, the date of discontinuation of tiaprofenic acid and any treatment of the ADR were reviewed. Data from reports prior to 1991 were aggregated. Estimated prescription data were obtained from the IMS MediPlusTM database and the reporting rate for each year calculated using estimates of total national prescriptions as the denominator.

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Results

Between 1 July 1981 and 31 December 1996 there were 1977 UK ADRs reported for tiaprofenic acid, relating to 1327 patients. Of these, 270 ADRs relating to 221 patients were considered relevant to cystitis. Table 1 shows the number of cases (ie, restricted to one ADR per patient) according to the year the report was received, the number of prescriptions and the new cases reported in each year (ie, those for which onset of the reaction was in that year).

There was a peak in reporting of cystitis-related disorders in 1994, with 87 reports, declining to 11 in 1996. The use of the drug in the UK has decreased from a peak in 1993 of around 300 000 prescriptions to about 170 000 in 1996. Table 2 shows the year of onset of cystitis-associated ADRs according to the year that the case was reported. Of 11 cases reported in 1996, in only three did the reaction start in that year.

The time between onset of the reported reaction and discontinuation of tiaprofenic acid is shown in table 3, according to the year in which the ADR started. The time to discontinuation appears to have shortened over the period examined, although in several cases the necessary data were not provided.

Table 2 Year of onset of ADR in relation to year reported to CSM/MCA

Year report received	Year of ADR onset						
	1982-90	91	92	93	94	95	96
1982-90	45						
1991	8	2					0
1992	4	6	3				4
1993	0	0	3	7			3
1994	7	9	9	25	20		17
1995	1	4	6	6	8	9	4
1996	0	1	1	1	1	3	3

Table 1 UK reports of urinary symptoms or cystitis received by CSM/MCA

Year report received	Reports received	Prescriptions $\times 10^3$	ADRs/ 10^5 prescriptions	ADR onset in year	New ADRs/ 10^5 prescriptions
1982-90	45	—	—	65	—
1991	10	237	4.2	22	9.2
1992	17	290	5.9	22	7.6
1993	13	310	4.2	39	12.6
1994	87	253	34.4	29	11.5
1995	38	201	18.5	12	6
1996	11	168	6.5	3	1.8
Not known	—	—	—	29	—

Table 3 Time from ADR onset to drug withdrawal in relation to year of onset (months)

Year of onset	Time to withdrawal: number of reports (%)			
	<3 mths	3 to <6 mths	6 to <12 mths	>12 mths
1992	3 (13.6)	1 (4.5)	2 (9.1)	16 (72.7)
1993	6 (16.7)	4 (11.1)	11 (30.5)	15 (41.7)
1994	12 (46.2)	5 (19.2)	7 (26.9)	2 (7.7)
1995	7 (70.0)	2 (20.0)	1 (10.0)	0
1996	2 (66.7)	1 (33.3)	0	0

Discussion

A broad approach to case definition was used: any symptoms associated with the lower urinary tract have been taken as indicating possible cystitis. Crawford and colleagues¹¹ reviewed UK reports of suspected lower urinary tract ADRs to tiaprofenic acid. The most frequent symptoms at presentation were increased frequency of micturition, dysuria, urgency, suprapubic pain and, occasionally, frank haematuria. The time to onset of symptoms after commencing tiaprofenic acid was very variable, with a long latency in many patients. In many instances, a drug association went unrecognised and treatment continued for long periods after onset of symptoms. Treatments for the ADR have included dimethylsulphoxide instillation, bladder dilatation, and corticosteroids. Several patients have required surgery, including cystectomy, ileal conduit urinary diversion, and pyeloplasty.

We would expect publicity regarding a new serious ADR to stimulate reporting: this is demonstrated by the peak in 1994. Many of these reports related to cases diagnosed in previous years: this is a recognised feature of ADR reporting following publicity or regulatory intervention. There has been a decline in reports of cystitis with tiaprofenic acid following the peak in 1994. This is partly due to decreased usage, as shown by prescription data but there has also been a fall in reporting rate for newly diagnosed reactions (table 1). Most reactions reported recently began some years ago (table 2); it should be noted that those starting more recently may not yet have been reported. There has been a trend towards earlier recognition in individual patients, as shown by reduced time to drug withdrawal (table 3). These findings are encouraging but do not provide complete reassurance that serious complications are being prevented.

Learning points

- tiaprofenic acid is associated with severe interstitial cystitis, sometimes requiring surgical intervention; the onset of symptoms may be delayed for months or years after starting the drug
- tiaprofenic acid should be withdrawn immediately if urinary symptoms occur
- delayed onset or 'latent' adverse reactions may easily go unrecognised
- it is important to report recognised adverse reactions if they lead to serious consequences (such as death, hospitalisation, or surgery)

An attempt was also made to review the treatment of reactions to see whether there was any trend towards milder reactions, with fewer requiring surgical intervention. Unfortunately, much of the information was unavailable. We attempt to follow up with reporters all serious ADRs where information is incomplete and this example highlights the importance of providing detailed information whenever requested.

Prescribers should remain alert to the occurrence of interstitial cystitis in patients receiving tiaprofenic acid, discontinue the drug immediately if symptoms arise, and report their suspicions through the Yellow Card scheme. It is important that doctors continue to report cases, as new characteristics of the association may be found and it is necessary to assess the effectiveness of precautions and warnings in the product information in limiting the time to diagnose the reaction and its severity.

Keywords: adverse drug reaction; tiaprofenic acid; cystitis; Yellow Card scheme

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