

Adverse Medication Events

Roaccutane (Isotretinoin) and the Risk of Suicide: Case Report and a Review of the Literature and Pharmacovigilance Reports

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INTRODUCTION

Approved for use by the U.S. Food and Drug Administration (FDA) in 1982, Roaccutane (isotretinoin, 13-*cis* retinoic acid), a member of the family of compounds called retinoids, is well recognized as an effective therapy for the treatment of severe recalcitrant acne. In addition, clinical use of the retinoids has demonstrated their effectiveness in acneiform eruptions, disorders of keratinization, and neoplasia.¹

The mechanism of the anti-acne action of isotretinoin is unknown. It is unique in its ability to affect, albeit not to the same degree, all the known etiological factors of acne: reduction of sebum production, lessening of comedogenesis, decreased surface and ductal colonization by *Propionibacterium acnes* and significantly diminished monocyte chemotaxis.²

Therapeutic response to isotretinoin is usually excellent. Unfortunately, it is not free of side effects. It is a well-known and potent teratogen. Other common side effects (more than 50% of patients) include

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cheilitis, xerostomia, epistaxis, facial erythema, headache, conjunctivitis, ocular irritation, alopecia, dizziness, arthralgias, and apathy. Less common side effects associated with and reported in temporal relation to the use of isotretinoin include pseudotumor cerebri (PTC), paronychia, inflammatory bowel disease, bone changes, corneal opacities, seizures, and cataracts. In common with other retinoids at pharmacological doses, isotretinoin causes elevation of serum lipids, particularly triglycerides.

The Irish license (package insert) for Roaccutane states the drug is indicated for severe nodulocystic acne that is nonresponsive to conventional therapy including systemic antibiotics and is available only as a hospital-only prescription. However, many dermatologists believe it is time to reduce these restrictions to include use of isotretinoin for mild and moderate acne and advise early use of isotretinoin irrespective of the severity of the complaint.²⁻⁴ At the General Infirmary at Leeds, between 1983 and 1986, severe acne was the main indication for isotretinoin (79% of patients), which contrasts with current figures of 74% of patients with mild or moderate acne and only 16% with severe acne.³ Use of oral retinoids for other than the specified indication has been reported as well as prescription by unauthorized doctors.

HYPERVITAMINOSIS A

Isotretinoin, being an analog of Vitamin A (retinol), shares many of the side effects experienced with Vitamin A. Hypervitaminosis A is the condition resulting from an excess of retinol in the

body. Retinol binds to Retinol Binding Protein (RBP). When the amount of retinol present exceeds the capacity of RBP to bind to it, the excess retinol is bound by lipoprotein, and in this form, it has toxic effects.⁵ Typical symptoms of hypervitaminosis A include irritability, headache, fatigue, myalgia, vomiting, dry skin, and after prolonged exposure, PTC may occur.

The central nervous system (CNS) manifestation of Vitamin A intoxication was first described in 1856 by Elisha Kane, the Arctic explorer.⁶ Following ingestion of polar bear liver (later found to contain a high concentration of Vitamin A), he recorded symptoms of vertigo, headache, drowsiness, and irritability. Over the succeeding 140 years, case reports of the occurrence of acute schizophrenia or remitting psychosis associated with hypervitaminosis A^{7,8} have appeared in the European and U.S. literature. First described by Gerber et al. in 1954,⁹ PTC has long been documented to occur in association with Vitamin A administration.^{10,11} PTC has also been documented in association with isotretinoin therapy^{12,13} and with the use of the retinoid, etretinate.¹⁴ In 1972, Restak et al. reported a case of toxic psychosis in a patient following Vitamin A treatment (50,000 IU 2-3 times daily) for acne.¹⁵ Other reports of depression,¹⁶ lethargy and loss of interest in surroundings,¹⁷ insomnia and listlessness,¹⁸ profound daily fatigue,¹⁹ and irritability²⁰ in association with Vitamin A have been recorded.

CASE REPORT

A 21-year-old male was seen by his general practitioner (GP) in 1996. Acne

was present on his chin and shoulders and was graded as 0.5 (scale of 0-5). He was prescribed topical Clinimycin (Clindamycin—U.S.). One month later, an improvement in his acne was recorded and he was prescribed Minocin SA 100 mg/d for two months. At his request, he was referred to a dermatologist. His only concurrent medication was a Flixotide inhaler for asthma, which he had been using for a number of years. The dermatologist graded his acne at 2 (scale of 1-10), prescribed Roaccutane 60 mg/d and asked him to return in a month. While on treatment, he developed the usual side effects of cheilitis, xerostomia, facial peeling, and mild photophobia.

Prior to starting isotretinoin therapy, the patient was outgoing and happy. He had no personal history of depression, and there was no family history of affective disorders. During his consultations with the dermatologist, on no occasion did he report that the acne was causing him anxiety. However, beginning with the second month of treatment, his family and friends noticed a change in his personality and behavior. He became withdrawn and solitary, which was unusual for him. His family reported to the GP that they thought his appetite had decreased, he had lost interest in his usual activities, and he tired more easily than usual. He was not however, seen by his GP during this period. While on treatment, he was seen on two occasions by his dermatologist. During his fourth month of treatment, he committed suicide.

A coroner's court was convened 13 months after the patient's demise. The conclusion of the court was that the cause of death was suicide. A rider to the coroner's conclusion was added suggesting that more emphasis be placed on isotretinoin patient information and that further research should be carried out into these effects of isotretinoin.

ADVERSE DRUG REACTION REPORTS

Following the case reported above, the family of the decedent commissioned an investigation into the adverse experiences of isotretinoin. The author was a

part of the investigative team. A review of the literature and reported adverse reactions (ADRs) to this drug was carried out to discover whether other cases with similar features had been described in the literature.

A MEDLINE search of isotretinoin therapy and its effects on mood (1980-1998) revealed 24 cases of psychological distress associated with the use of this drug.²¹⁻²⁹ Many of these cases reported the subsequent emergence of depression with features similar to that of hypervitaminosis A. Suicide²² and attempted suicide²³ in association with isotretinoin therapy have also been reported.

A study in 1983 showed 5.5% (6/110) of patients with acne experienced depressive symptoms, as evidenced by the occurrence of malaise, crying spells, and forgetfulness within two weeks of commencing isotretinoin.²⁴ Meyskens also noted similar psychological changes in patients with cancer treated with 3 mg/kg/d isotretinoin.²⁵ The ADR Reporting System of the American Academy of Dermatology received reports of 104 suspected adverse reactions to isotretinoin between October 1982 and June 1985,²⁶ of which CNS represented 22.1% (23/104), second only to skin and mucous membrane reactions (27.9%, 29/104). These CNS reactions included headache, depression, dizziness, and personality disorder. The relationship of depression to isotretinoin therapy was confirmed by rechallenge (Scheinman et al.²⁷) that reported that 1% (7/700) of patients treated with oral isotretinoin developed depressive symptoms, the severity of which interfered with their normal functioning. This relationship was also confirmed by Villalobos et al.²⁸ Byrne et al.²⁹ described the persistence of depressive symptoms that required active treatment in three patients following cessation of isotretinoin. Despite the recurrence of acne in one of the patients, follow-up showed no depressive symptoms.

Concerns about the safety of isotretinoin have been raised in the past. In 1998, reports surfaced in the media associating this drug with suicides (one in Ireland; two in the UK; two in the U.S.A.)

and attempted suicides (one in the UK; one in the U.S.A.).

In addition to Roaccutane, ADRs for five of the most commonly prescribed anti-acne treatments (Dianette, doxycycline, minocycline, oxytetracycline, and tetracycline) were reviewed. ADR data was obtained from the World Health Organization (WHO), UK Medicines Control Agency (MCA), and the manufacturer, Roche. The search for ADRs listed under Dianette included searches carried out under its active ingredients (ethinylestradiol and cyproterone).

Based on the available information, there were more reports of psychiatric adverse events and suicide from isotretinoin than from the use of the other five acne therapies combined (Table 1). Worldwide, 1,830 reports of psychiatric events attributable to these six medications were identified, of which isotretinoin was implicated in 59.8% (1095/1830). Second to this was minocycline, implicated in 14.2% (261/1830). Forty-seven and 56 cases of suicide and suicidal ideation were reported in association with the use of Roaccutane, respectively, with none being reported for the other medications. Of 75 cases of attempted suicide reported, 89.3% (67/75) were associated with the use of isotretinoin, with 4% (3/75) associated with the use of both Dianette and tetracycline, and 2.6% (2/75) for minocycline. ADR data for the UK (Table 2) reflect a similar pattern, with 51.5% (135/262) of psychiatric ADRs attributed to isotretinoin. In addition, all cases of suicide/suicide attempt/suicide ideation were associated with the use of this medication. The source for this data relies on voluntary reporting and probably represents significant underreporting.

Table 3 shows the number of prescription items dispensed in England from 1982 to 1997. Isotretinoin, while attracting the largest percentage of psychiatric ADRs, had the lowest number of prescriptions issued (12,400). During this period, 1,214,600 prescriptions were dispensed for Dianette. The indication in 184,200 cases was given as acne. Dianette was implicated in only 1.9% (5/262) of psychiatric ADRs.

Table 1. Worldwide Psychiatric ADR Reports

| Medication | Extract Period | Psychiatric ADRs (% of total) | Suicide | Suicide Attempt | Suicidal Ideation |
|------------------------------|----------------|-------------------------------|---------|-----------------|-------------------|
| Roaccutane ^a | 1982-1998 | 1095 (59.8%) | 47 | 67 | 56 |
| Minocycline ^b | 1971-1998 | 261 (14.2%) | 0 | 2 | 0 |
| Doxycycline ^b | 1965-1998 | 213 (11.6%) | 0 | 0 | 0 |
| Tetracycline ^b | 1964-1998 | 169 (9.2%) | 0 | 3 | 0 |
| Dianette ^b | 1980-1998 | 55 (3%) | 0 | 3 | 0 |
| Oxytetracycline ^b | 1965-1998 | 37 (2%) | 0 | 0 | 0 |

^aRoche Laboratories Ltd. Ireland, cutoff date May 31, 1998.

^bWHO Data, cutoff date August 1998.

Table 2. UK ADR Data (Source: MCA)

| Medication | Psychiatric ADRs (% of total) | Extract Period | Suicide | Suicide Attempt | Suicidal Ideation |
|-------------------------|-------------------------------|----------------|---------|-----------------|-------------------|
| Roaccutane ^a | 135 (51.5%) | 1963-1999 | 9 | 8 | 6 |
| Minocycline | 45 (17.1%) | 1973-1998 | 0 | 0 | 0 |
| Tetracycline | 32 (12.2%) | 1964-1998 | 0 | 0 | 0 |
| Oxytetracycline | 23 (8.7%) | 1965-1998 | 0 | 0 | 0 |
| Doxycycline | 22 (8.3%) | 1965-1998 | 0 | 0 | 0 |
| Dianette | 5 (1.9%) | 1987-1998 | 0 | 0 | 0 |

^aData for Roaccutane, cutoff date July 1999.

^bEarliest reaction date: February 15, 1983.

Table 3. Prescription Data (England 1982-1997)

| Medication | Prescriptions ^a (x1000) | Indication, Acne |
|-----------------|------------------------------------|------------------|
| Tetracycline | 147,237.0 | |
| Oxytetracycline | 31,301.7 | |
| Doxycycline | 13,650.0 | |
| Minocycline | 8,802.9 | |
| Dianette | 1,214.6 | 184.2 |
| Isotretinoin | 12.4 | 12.4 |

^aData provided by Dept. of Health, Statistics Division 1E, Prescription Cost Analysis System.

Minocycline is used extensively in the treatment of acne vulgaris (8,802,000 prescriptions issued between 1982–1997). Between 1970–1997, 6.5 million patients³⁰ were treated with minocycline in the UK. A total of 45 psychiatric adverse events were received by the MCA between 1973 and 1997. Roaccutane has a UK patient exposure of 50,000 (8 million worldwide, PharmaFocus data) and has received reports of 135 psychiatric adverse events. Based on these figures, the incidence rates of psychiatric adverse reactions for Roaccutane and Minocycline are 270 and 0.692 per 100,000 people treated, respectively. These medications (with the exception of Roaccutane) are used to treat conditions other than acne. As it was not possible to obtain patient exposure data for these medications where the indication was acne, the frequency of psychiatric reactions attributable to these medications, in the population of acne patients, could not be calculated.

Other authors have suggested that the association between isotretinoin and psychiatric morbidity is unlikely to be causal, attributing the depressive symptoms to the presence of acne. Cotterill and Cunliffe³¹ suggest that dermatological patients are at greater risk of suicide and suggest early use of isotretinoin to reduce this risk. However, their findings are open to an alternative interpretation. All but one of the cases they described had long-standing psychiatric illness (manic depression, alcoholism) or other risk factors for psychiatric morbidity (recently bereaved) prior to being seen by the authors.

REVISED LABEL INFORMATION

On February 25, 1998, the FDA issued a Talk Paper declaring new safety information regarding isotretinoin, as a result of adverse event reports the agency had received. The revised information leaflet now reads "Psychiatric disorders: Accutane may cause depression, psychosis and, rarely, suicide ideation, suicide attempt and suicide. Discontinuation of Accutane therapy may be insufficient; further evaluation may be necessary. . . .

Of the patients reporting depression, some reported that the depression subsided with discontinuation of therapy and recurred with reinstatement of therapy." Earlier information leaflets read "depression has been reported in some patients on Accutane therapy. In some of these patients, this has subsided with discontinuation of therapy and recurred with reinstatement of therapy."

Almost one year prior to this U.S. package insert revision, the French product label was altered on March 3, 1997, to include "suicide attempt" as a side effect of isotretinoin therapy,³² and reads, "In rare occasions, neuropsychological problems have been recorded (behavioral difficulties, depression, convulsions and suicide attempts)." This revision was introduced in France as a result of the findings of a prospective national inquiry (1993–1994) in which Roche and more than 2,000 state dermatologists participated. The inquiry was initiated following a paper presentation that reported on a suicide associated with isotretinoin therapy.²³ The results of the inquiry were presented at the Third Forum of the National and Provincial Journal of Dermatology at Montpellier (March 14–17, 1996) but were never published. Revised warnings have now been introduced in Ireland (May 1998) and the UK (April 1998).

SUMMARY AND RECOMMENDATIONS FOR PRACTITIONERS

In view of the increasing concerns regarding the potential of this compound to cause depression, further research is required to allow this association to be fully evaluated. Dermatologists and other prescribing physicians should be well aware of this potential life-threatening adverse event, drug indications should be adhered to (don't use when less toxic drugs will suffice), and patients should be thoroughly screened and evaluated for signs of depression on a frequent and regular basis during therapy. Pharmacists should include this important warning in their counseling of patients who use isotretinoin and their families.

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