

Affective psychosis following Accutane (isotretinoin) treatment

Yoram Barak^{a,c}, Yonit Wohl^{b,c}, Yifa Greenberg^a, Yosefa Bar Dayan^b, Tali Friedman^b, Gideon Shoval^a and Haim Y. Knobler^{a,d}

Isotretinoin (Accutane) ranks in the top 10 of the US Food and Drug Administration's database of drugs associated with reports of depression and suicide attempts. However, this association is still controversial because up to 5.6% of patients with moderate acne may have pre-existing suicidal ideations, improvement of acne often reduces associated depression, and isotretinoin users are reportedly no more likely than those taking antibiotics for acne to have depression or commit suicide. We describe a series of cases of manic psychosis that developed in a 1-year period (2003) in association with isotretinoin treatment and resulted in suicidality and progression to long-standing psychosis. Cases were drawn from 500 soldiers who had been evaluated in a military specialists dermatology clinic for severe acne. Data were summarized from medical records of five severe acne patients treated by isotretinoin during their compulsory military service. Data from their draft board examinations and service records, as well as repeated clinical assessments by certified psychiatrists at the Israel Defense Forces (IDF) Mental Health Department clinic, were evaluated. Five young adults developed manic psychosis within a mean of 7.6 months of exposure to isotretinoin. In three cases, this was accompanied by a

suicide attempt, and in three cases, psychosis lasted for longer than 6 months. Either a personal history of obsessive-compulsive disorder, neurological insult or family history of a major psychiatric illness were present in all cases. The present case-series is suggestive of an increase in the likelihood of an association between exposure to isotretinoin and manic psychosis. Associated risk factors were both family and personal history of psychiatric morbidity. Further studies are needed to establish our findings. *Int Clin Psychopharmacol* 20:39–41 © 2005 Lippincott Williams & Wilkins.

International Clinical Psychopharmacology 2005, 20:39–41

Keywords: Isotretinoin, mania, military, psychosis, suicide

^aMental Health Department, ^bMedical Assessment Branch, Medical Corps, IDF, Israel, ^cSackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv and ^dHadassah Hebrew University Medical School, Jerusalem, Israel.

Correspondence and requests for reprints to Dr Yoram Barak, Psychogeriatric Department, Abarbanel Mental Health Center, 15 KKL Street, Bat-Yam, Israel. Tel: + 972 355 52738; e-mail: mdybarak@netvision.net.il

Received 23 July 2004 Accepted 1 November 2004

Introduction

Isotretinoin (Accutane; Hoffmann-La Roche, Basel, Switzerland) is a drug resembling the chemical structure of vitamin A that is indicated for moderate to severe recalcitrant forms of acne. This lipid-soluble compound affects the central nervous system and reports of intracranial hypertension, depression and suicidal ideation have been published subsequent to its marketing in the USA in 1982 (O'Donnell, 2003).

Although the exact mechanism of action of isotretinoin is still obscure, studies performed *in vivo* in animals show specific high expression of retinoid receptors and cellular binding proteins in dopamine innervated pathways, especially the striatum, pointing to their possible involvement in the pathogenesis of different psychiatric disorders (Zetterstrom *et al.*, 1999).

Despite serious side-effects and adverse events, the use of isotretinoin in the last 8 years (until 2000) has increased by 2.5-fold (250%), as reflected by the number of dispensed prescriptions (Wysowski *et al.*, 2002).

0268-1315 © 2005 Lippincott Williams & Wilkins

The growing number of reported cases of depression and suicide associated with isotretinoin use in patients with acne has prompted concern among care givers, as well as among patients and their relatives, and has triggered repeated warnings from government regulators. Recently, the Canadian Medical Association issued a health and drug alert entitled 'Accutane (isotretinoin) and psychiatric adverse effects' (Wooltorton, 2003). The reason for posting this alert was the possible link with depression and suicide, as well as the warning that people taking isotretinoin may also experience aggressive and violent behaviour.

The aim of the present report is to add to the growing body of data. We provided a description of five consecutive cases during a 1-year period wherein suicidality and affective, long-standing psychosis occurred within months in young army conscripts after exposure to isotretinoin.

Methods

During the period January to December 2003, all cases of psychosis associated with exposure to isotretinoin among

Table 1 Demographic and clinical variables

Gender	Age (years)	Military occupation	Lag time (months)	Predisposing factors	Psychiatric diagnosis ^a
Female	20	Technical sector	3	OCD	Schizophreniform Suicide attempt
Male	19	Technical sector	8	OCD	Schizoaffective Suicide attempt
Female	19	Technical sector	7	Family: schizophrenia OCD	Schizophreniform
Female	20	Technical sector	11	Family: schizophrenia Pituitary adenoma	Schizoaffective
Male	20	Administrative sector	10	Family: bipolar Intractable headache	Schizoaffective Suicide attempt

^aAll diagnoses were made according to DSM-IV. Lag time = time in months between administration of isotretinoin and development of psychosis. OCD, Obsessive-compulsive disorder.

conscripts who were serving their compulsory army service were reviewed at an Israel Defense Forces (IDF) Mental Health Department clinic. The clinic serves as a tertiary care centre.

During the study period, 500 conscripts were seen by a dermatologist for severe acne and the cases described here are drawn from this cohort. There were five cases: two male and three female; mean age 19 ± 1.2 years. All had undergone the draft board assessment before service, at the age of 17 years (Reichenberg *et al.*, 2002).

In brief, the assessment consists of (i) a physical examination, a review of systems and psychiatric history, which were all conducted by a physician; (ii) assessment of language ability; (iii) a battery of tests measuring intellectual functioning; and (iv) a structured interview assessing personality and behavioural traits. None of these screening tests was positive for any of the conscripts before or at the time of their recruitment.

Results

Demographic and clinical data for the five soldiers are presented in Table 1.

All five soldiers were treated with isotretinoin for acne prior to the development of psychiatric morbidity. Mean lag time from intake of isotretinoin to occurrence of psychosis was 7.6 ± 4.2 months. In all cases, the psychotic episode had lasted longer than 3 months and, in three of the cases, psychosis lasted longer than 6 months. Manic irritability was noted in all cases. Three of the soldiers had attempted suicide by jumping from a moving vehicle, cutting wrists or administering a self-inflicted abdominal penetrating wound with a sharp object. All received psychiatric treatment, three as inpatients, before their discharge from the army due to their psychiatric morbidity. Psychopharmacological treatment consisted of second generation antipsychotic medications (risperidone in two cases and olanzapine in three cases). Response to treatment was assessed using the 7-point Clinical Global Impression (CGI) scale. In four cases, the

response was scored as 'good' or 'very good' whereas, in one soldier, only 'very little' response was observed even after 6 months of treatment.

All patients had a personal or family history of psychiatric or neurological morbidity. In three cases, obsessive-compulsive symptomatology was treated at the age of 16 years. In one case, a pituitary adenoma was treated with decapeptide and another conscript was treated by anticonvulsants due to intractable headache following closed head trauma. In three of the cases, family history revealed a bipolar disorder in a first degree relative and, in one of these cases, a sister had developed a manic episode following isotretinoin treatment at the age of 18 years.

Discussion

Isotretinoin is a retinoid that is approved for the treatment of cystic acne, although its indications for use have been constantly extended to include milder cases. There has been a growing interest in the possible association between isotretinoin use and increased risk of depression and suicide. However, this issue remains controversial (Bremner, 2003).

A growing number of case reports have addressed the association between exposure to isotretinoin, depression and suicidality, with two prominent reviews having been published recently (Jacobs *et al.*, 2001; Ng and Schweitzer, 2003). Both reviews concluded that: '... causal relationship between isotretinoin therapy and depression has not been clearly established ... depression can occur as an idiosyncratic side-effect ...'. By contrast to these conclusions, the FDA's adverse event report data base, including dechallenge and challenge cases, demonstrated some support for the speculated link (Hull and D'Arcy, 2003).

Although case report series are inconclusive, two large retrospective cohort studies, both of them sponsored by Hoffman La Roche, concluded that their results did not support an association between the use of isotretinoin and the onset of depression or psychosis (Hersom *et al.*,

2000; Jick *et al.*, 2003). Major drawbacks, as well as different interpretations of the results, are presented in a recent review (Hull and D'Arcy, 2003).

Given our observations suggestive of an increase in the likelihood of an association between the development of affective psychosis and the diathesis of the five reported cases, we suggest that screening and identifying those patients who are at high risk of psychopathology is carried out before isotretinoin administration is undertaken, especially in stressful settings such as military service.

References

- Bremner JD (2003). Does isotretinoin cause depression and suicide? *Psychopharmacol Bull* **37**:64–78.
- Hersom K, Neary MP, Levaux HP, Klaskala W, Strauss JS (2000). Isotretinoin use and risk of depression, psychotic symptoms, suicide, and attempted suicide. *Arch Dermatol* **136**:1231–1236.
- Hull PR, D'Arcy C (2003). Isotretinoin and antidepressant pharmacotherapy: a prescription sequence symmetry analysis. *J Am Acad Dermatol* **49**:424–432.
- Jacobs DG, Deutsch NL, Brewer M (2001). Suicide, depression, and isotretinoin: is there a causal link? *J Am Acad Dermatol* **45**:S168–S175.
- Jick SS, Kremers HM, Vasilakis-Scaramozza C (2003). Isotretinoin use and subsequent depression and suicide: presenting the evidence. *Am J Clin Dermatol* **4**:493–505.
- Ng CH, Schweitzer I (2003). The association between depression and isotretinoin use in acne. *Aust NZ J Psychiatry* **37**:78–84.
- O'Donnell J (2003). Overview of existing research and information linking isotretinoin (accutane) depression, psychosis, and suicide. *Am J Ther* **10**:148–159.
- Reichenberg A, Weiser M, Rabinowitz J, Caspi A, Schmeidler J, Mark M, *et al.* (2002). A population-based cohort study of premorbid intellectual, language, and behavioral functioning in Patients with schizophrenia, schizoaffective disorder, and nonpsychotic bipolar disorder. *Am J Psychiatry* **159**:2027–2035.
- Wooltorton E (2003). Accutane (isotretinoin) and psychiatric adverse effects. *JAMC* **168**:66.
- Wysowski DK, Swann J, Vega A (2002). Use of isotretinoin (Accutane) in the United States: rapid increase from 1992 through 2000. *J Am Acad Dermatol* **46**:505–509.
- Zetterstrom RH, Lindquist E, Mata de Urquiza A, *et al.* (1999). Role of retinoids in the CNS: differential expression of retinoid binding proteins and receptors and evidence for presence of retinoic acid. *Eur J Neurosci* **11**:407–416.