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CASE REPORT/CASE SERIES

Acne, Isotretinoin Treatment and Acute Depression

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Summary

The association between isotretinoin therapy and depressive symptoms in acne patients has generated much recent interest but has not been systematically explored.

A 17-year-old man with acne vulgaris developed symptoms of acute depression two weeks after beginning isotretinoin therapy. The depressive symptoms improved with reduction of isotretinoin dose and treatment with sertraline. Of note, however, is that when the isotretinoin dose was again increased, the depressive symptoms recurred despite clearing of the skin, leading to an unsuccessful suicide attempt. Isotretinoin was finally discontinued and the depression rapidly resolved. Although the effects of hypervitaminosis A may be involved aetiologically, the predictive factors of drug-related depression remain unclear. Significant depressive symptoms that develop during the course of treatment need close monitoring and may necessitate both antidepressant therapy and discontinuation of the drug. Given the uncertain causal relationship between isotretinoin and depression, versus the potential psychological benefits of effective acne treatment, systematic studies exploring the impact of isotretinoin on mood are needed.

Key words: *acne, isotretinoin, depression, suicide, causal relationship.*

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Introduction

Acne is a common condition affecting young patients. A significant proportion of those with moderate to severe acne is treated with systemic isotretinoin, particularly if there are concerns about facial and bodily appearance. Isotretinoin, a vitamin A derivative (13-cis-retinoic acid), is a highly effective treatment for cystic acne. While side effects like dry skin, photosensitivity, lethargy and abnormal liver and lipid functions are well known (Wolverton 1991), its effect on mood is less well documented. Severe depression can develop for the first time following isotretinoin use in a subgroup of patients, as is highlighted by the following case.

Concern about depression associated with isotretinoin use from numerous reports has led to much recent publicity linking the risk of depression and other psychiatric effects with isotretinoin. The Adverse Drug Reactions Advisory Committee has received at least 12 reports since 1986 of depression related to isotretinoin in Australia (ADRAC 1998). Furthermore, the U.S. Food and Drug Administration has reported about 24 cases where depression resolved when therapy was ceased but recurred when treatment was reintroduced (Ault 1998). Consequently, product information was recently changed, warning that isotretinoin may cause depression, psychosis, and rarely suicidal ideation, suicide attempts and suicide.

Recently a retrospective cohort study of 7535 isotretinoin users from two large population health databases found no increase in relative risk estimates for depression, psychotic symptoms, suicide and attempted suicide (Jick et al 2000). Despite having the largest data set yet published, the study remains inconclusive because of methodological limitations including the retrospective study design, use of a computerised database, inadequate method used for case recognition and lack of psychometric measures. Significant variables like severity of acne, treatment compliance, concomitant medications and comorbid conditions were not adequately controlled. It is also possible that anecdotal case reports may be picking up a small subgroup of patients at risk of developing depression but too few to show significant differences in systematic studies.

Case report

We report the case of a 17-year-old male who

developed acute depression and suicidal ideation during a course of treatment with isotretinoin for moderately severe facial acne vulgaris. The patient was previously a well adjusted and active adolescent although he had been self-conscious about the facial acne he suffered for the last five years. He had no premorbid history of any psychiatric problems but there was a family history of post-natal depression. Despite previous topical treatment with adapalene 0.1% gel and azelaic acid 5% cream, and 18 months therapy with antibiotics (doxycyline hydrochloride), he still had moderate inflammatory acne consisting of multiple papules, pustules and comedones. After discontinuing the topical therapy and antibiotics he was immediately commenced on isotretinoin (0.63 mg/kg/day) for the first time following normal routine physical and laboratory examination. About two weeks into treatment he began to develop depressive symptoms over several weeks which included irritability, insomnia, decreased appetite, lack of motivation and interest, social withdrawal and suicidal ideation. Subsequently, his family reported that after the onset of depression, he had angry outbursts related to alcohol use that had not previously occurred. He also stopped his regular attendance to both school and the gym.

His isotretinoin dose was reduced (0.32 mg/kg/day) for two weeks and he was commenced on sertraline 50 mg, which was gradually increased to 150 mg. He responded to sertraline and his symptoms further improved with the support of his general practitioner and a counsellor. However, he also had high expectations of the anti-acne drug and became disappointed when the skin dryness he experienced (a side effect of isotretinoin) had temporarily worsened his facial appearance. As his self consciousness about his skin may have been aggravating his depression, the higher isotretinoin dosage was resumed to treat his acne and help alleviate any negative psychological impact. After another two weeks, the patient further increased the dose of isotretinoin (1.0 mg/kg/day) to achieve a more rapid and effective response.

However, three months into treatment his mood deteriorated and the depressive symptoms relapsed, despite significant improvement of his skin status and being compliant with sertraline. He was not enjoying his casual work and he felt increasingly frustrated and hopeless. Consequently, he planned and attempted suicide by ingesting a substantial overdose of pseudoephedrine and diazepam, medications that belonged to his parents. Fortunately his family found him and he was treated at the local emergency department.

Following discharge to the care of his general practitioner, he was referred to a consultant psychiatrist who confirmed the diagnosis of severe major depressive disorder associated with isotretinoin treatment (Hamilton Depression 17-item scale score of 28). The patient was maintained on sertraline at 150 mg but isotretinoin was ceased. Altogether he had taken 7200mg (11.4mg/kg) of isotretinoin. At the time of discontinuation of isotretinoin, his skin was clear and it did not worsen subsequently. Over the next two weeks his mood, sleep, appetite, energy levels and motivation improved rapidly and he was no longer suicidal. After six weeks, he reported no depressive symptoms and had returned to normal functioning, working full time and attending the gym regularly.

Discussion

Data from the current literature on the possible association between isotretinoin and depression is mostly limited to brief anecdotal case reports published in non-psychiatric journals (Scheinman et al 1990; Gatti and Serri 1991; Feck et al 1991; Beylard et al 1991; Hazen et al 1983). One study reported spontaneous depression in 1% out of 700 patients participating in a clinical trial with isotretinoin, which was unrelated to dosage (range of 0.3 to 1.3 mg/kg/day) or period of exposure (Scheinman et al 1990). The depressive symptoms resolved rapidly within two to seven days after cessation of isotretinoin. The authors suggested that depression is a rare idiosyncratic adverse effect that may develop during isotretinoin therapy in predisposed patients. Another report raised concern about the severity of such drug-induced depressive illness particularly affecting younger patients, quoting cases of reported suicides involving mainly patients aged under 18 (Byrne and Hnatko 1995). Anecdotal studies also suggest that total discontinuation of the drug may be a necessary condition for sustained recovery from depression (Anit 1998; Bravard et al 1993; Scheinman et al 1990). Crying spells, irritability, malaise and headache can be produced by benign intracranial hypertension related to hypervitaminosis A associated with treatment with retinoids (Scheinman et al 1990; Byrne and Hnatko 1995). The similarities to these neuropsychiatric symptoms and the drug challenge/rechallenge data implicate possible mechanisms involved in isotretinoin-induced depression.

Clinicians should assess the risk factors and past history of depression prior to prescribing isotretinoin, although the predictive factors of drug-related major depression remain uncertain. Any depressive symptoms that develop during the course of treatment need close monitoring and may require prompt psychiatric assessment. Significant depression may necessitate both discontinuation of the drug and further evaluation for antidepressant therapy. Resolution of depression associated with isotretinoin appears to be rapid and complete with appropriate treatment.

On the other hand, severe acne, especially in adolescents and young adults, is frequently associated with depression, anxiety, low self esteem, body image problems, self consciousness, lack of self-confidence, social withdrawal and psychological distress (Gupta and Gupta 1998; Koo 1995). Hence effective acne treatment is likely to result in a positive psychological outcome (Kellett and Gawkrodger 1999; Rubinow 1987; Macdonald Hull et al 1991) and better quality of life. However, in the above case, the depression worsened despite clearing of the acne. Another aspect relates to possible unrealistic expectations following treatment that the clearing of the disfiguring skin condition would lead to resolution of personal and social inadequacies (Gatti and Serri 1991; Peck et al 1991). Such unfulfilled hopes may heighten the sense of failure previously attributed to the acne and precipitate depression.

Given the uncertain causal relationship between isotretinoin and depression, versus the potential psychological benefits of effective acne treatment, carefully designed systematic studies exploring the impact of isotretinoin on mood are needed. A prospective study comparing the effect on depressive symptoms and quality of life in patients treated with isotretinoin versus those treated with antibiotic or topical therapies is currently being conducted to further clarify these issues (Ng et al, unpublished data).

References

Adverse Drug Reactions Advisory Committee (ADRAC) (1998) Depression and isotretinoin. Australia Adverse Drug Reactions Bulletin 17: 11.

Ault A (1998) Isotretinoin use may be linked with depression. The Lancet 351: 730.

Bravard P, Krug M, Rzeznick JC (1993) Isotretinoine et depression, soyons vigilantes. Nouv Dermatol 12: 215.

Byrne A, Hnatko G (1995) Depression associated with isotretinoin therapy. Can J Psych 40: 562.

Gatti S, Serri F (1991) Acute depression from isotretinoin. J Am Acad Dermatol 25: 132.

Gupta MA, Gupta AK (1998) Depression and suicidal ideation in dermatology patients with acne, alopecia areata, atopic dermatitis and psoriasis. Br J Dermatol 139: 846-850.

Hazen PG, Carney JF, Walker AE, Stewart JJ (1983) Depression a side effect of 13-cis-retinoic acid therapy. J Am Acad Dermatol 6: 278-279.

Jick SS, Kremers HM, Vasilakis-Scaramozza C (2000) Isotretinoin use and risk of depression, psychotic symptoms, suicide, and attempted suicide. Arch Dermatol 136: 1231-1236.

Kellett SC, Gawkrodger DJ (1999) The psychological and emotional impact of acne and the effect of treatment with isotretinoin. Br J Dermatol 140: 273-282.

Koo J (1995) The psychosocial impact of acne patients' perception. J Am Acad Dermatol 32 (Suppl): 26-30.

Macdonald Hull S, Cunliffe WJ, Hughes BR (1991) Treatment of the depressed acne dysmorphophobic acne patient. Clin Exp Dermatol 16: 210-211.

Peck GL, DiGiovanna JJ, Rubinow DR (1991) Acute depression from isotretinoin therapy. J Am Acad Dermatol 25: 132.

Rubinow DR, Peck GL, Squillace KM, Gantt GG (1987) Reduced anxiety and depression in cystic acne patients after successful treatment with isotretinoin. J Am Acad Dermatol 17: 25-32.

Scheinman PL, Peck GL, Rubinow DR, DiGiovanna JJ, Abangan DC, Ravin PD (1990) Acute depression from isotretinoin. J Am Acad Dermatol 22: 1112-1114.

Wolverton SE (1991) Retinoids. In: Wolverton SE, Wilkings JK (eds) Systemic drugs for skin disease. WB Saunders, Philadelphia, pp 187-218.