Isotretinoin therapy and depression – evidence for an association

Alan Byrne, Morgan Costello, Elaine Greene, Terry Zibin

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Abstract

Objectives: The object of this paper is to evaluate the evidence suggesting an association between the use of the anti-acne agent isotretinoin and the subsequent development of depression.

Method: Three case histories of individuals who had received treatment with isotretinoin and subsequently developed depression are reviewed.

Results: All three individuals were noted to have a depressive illness which was notable by the prominence of symptoms of irritability, agitation and aggression.

Conclusions: The indications from the three cases described suggest that there appears to be an association between depression and the recent use of isotretinoin. This may relate to the ability of isotretinoin to simulate hypovitaminosis A, with aggression, irritability and depression as a direct result of this effect. Young males may be particularly prone to developing this response.

Key words: Isotretinoin; Depression; Agitation; Aggression.

Introduction

The use of systemic retinoid therapy for the treatment of acne has become an accepted form of treatment, especially for severe nodular or inflammatory acne, acne conglobata and recalcitrant acne.[1] In addition to the well known teratogenic potential of these compounds, there is also a significant number of other side-effects which have been associated with the use of these agents. These include cheilitis, conjunctivitis, alopecia, regional ileitis, corneal opacities, gastrointestinal bleeding, lipid abnormalities and central nervous system disorders such as pseudo-tumour cerebri, dizziness and apathy.[2-4] The occurrence of pseudo-tumour cerebri has been noted, particularly in association with the use of tetracycline therapy [4], but the other side-effects have been associated with the use of retinoids alone. This paper describes the features of three young patients who presented with severe depressive symptoms associated with isotretinoin therapy, and in two of the cases the depression was of life threatening proportions. We feel that it is important, therefore, that psychiatrists are aware of the potential dangers of retinoid therapy, as the use of retinoids will doubtless increase in the coming years, and more cases of depression are likely to present. As the use of retinoids is specific to dermatology practice, and as these patients may present for psychiatric care, the potential hazards related to the use of this group of compounds may be unknown to psychiatrists. The previous reports of depression in association with isotretinoin have been described as idiosyncratic,[5] and have been said to respond to withdrawal of the compound, but it is our contention that the adverse psychological sequelae of these compounds may be more persistent than previously believed, and indeed may be life threatening. Media attention has been drawn to the plight of a number of young individuals said to have suffered greatly as a result of treatment with retinoids, but Goulden *et al*[6] have gone to some lengths to discredit this report, and have denied that an association exists between depressive symptoms and the use of oral retinoids such as isotretinoin. We believe, however, that an association does exist between depression and the use of isotretinoin for the treatment of acne and the cases reported here add weight to this belief. We believe that this is one of the first reports of such an association to appear in the psychiatric literature.

*Alan Byrne, BA, MS, MRCPI, MRCPsych, Consultant psychiatrist, Naas General Hospital, Naas, Co Kildare, Ireland.
Morgan Costello, MS, BCh, BAO, Registrar, St Loman's Hospital, Palmerstown, Co Dublin, Ireland.
Elaine Greene, BA, MS, BCh, BAO, Registrar, Eastern Health Board Mental Handicap Service, Ballyboden, Dublin 14, Ireland.
Terry Zibin, (Social Worker), Alberta Hospital Ponoka, Alberta, Canada.
*Correspondence

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Case 1

Ms A, a 28 year old woman, was referred for assessment of low mood agitation and features of depression. The symptoms had been present for several months, and the agitation and irritability had led to the breakup of her marriage some eight months prior to the interview. At interview Ms A described disturbed sleep, decreased appetite, reduced concentration, anhedonia, early morning wakening and increasing levels of irritability. The irritability took the form of tirades of verbal abuse directed towards family members, without apparent cause. Ms A scored 26 on the Hamilton Rating Scale.[8] Previous psychiatric history revealed a two year history of mild anorexic symptoms in the late teens, which had resolved without psychiatric intervention. There was no previous history of depression, and no family history of affective disorders. Other history revealed a four month period of treatment with isotretinoin for cystic acne this had been received 10 months prior to the consultation, and the episodes of intense irritability which led to the marital breakdown had begun during the course of the isotretinoin treatment.

A course of imipramine was commenced, and Ms A responded well to the addition of the antidepressant therapy, with a gradual improvement in her mood and her ability to function in social situations. On review after five weeks of treatment, Ms A was significantly brighter and scored nine on the Hamilton Rating Scale. Her ability to enjoy life had also improved, and her sleep pattern had stabilised. She has returned to work, and is appreciably better several months into treatment.

Case 2

Mr B an 18 year old man, was admitted to our unit following an attempt on his life by taking an overdose of trazadone tablets. Mr B described a three month history of deteriorating mood, with loss of interest, apathy, insomnia, anergia, and anhedonia, and marked irritability had also been noted. This increased irritability had culminated in an amount of family disruption and caused prominent guilt feelings in the patient. There had also been a marked deterioration in the patients school performance and social functioning. At interview he presented as depressed, agitated and hopeless. He described decreased appetite, decreased sleep and reduced energy, and he scored 31 on the Hamilton Depression Scale. There was no previous history of psychiatric problems, no family history of depression, and there were no obvious psychosocial stressors in the previous year. At the time of admission Mr B was receiving isotretinoin therapy for cystic acne, and had been taking this for a period of five months prior to his overdose. He had been receiving trazodone therapy for his depression for the previous six weeks, without appreciable benefit.

He was commenced on fluoxetine therapy, his retinoid therapy was stopped, and a gradual improvement in his mood was noted over the next four weeks. Upon review as an outpatient he is euthymic and despite the recurrence of his acne his score on the Hamilton Scale is now five.

Case 3

Ms C, a 20 year old woman, was referred for assessment of depression, tearfulness and suicidal ideation, which had been present for several weeks. Admission to hospital was indicated on the basis of persistent suicidal ideation with pronounced feelings of worthlessness and agitation, anergia and anhedonia noted at interview. These symptoms of depression had been worsening over the months prior to the consultation. She also described increasing levels of irritability and angry outbursts directed towards family members. The patient scored 29 on the Hamilton Depression Scale at the initial interview. Ms C had no previous history of depression prior to this episode, and neither was there a family history of affective disturbance. She complained of a severe headache which had been present for several weeks, but neurological investigation was normal. Ms C had been receiving isotretinoin therapy, for an acne condition intermittently during the previous year, and this was continuing, as the dermatological response had been excellent.

Following admission, Ms C was commenced on imipramine and the acne therapy was discontinued. Her response to medication was poor, and trials of other antidepressants were equally unsuccessful. Ms C became increasingly irritable, and eventually upon confrontation she revealed that she had continued to take her own supply of isotretinoin whilst in hospital. This medication was stopped, and therapy with fluoxetine was continued. The patient's mood improved considerably, and she was fit for discharge after a further two weeks. Her mood has continued to stabilise, and interactions with the family have improved greatly. On review her mood is normal, the headache has disappeared, and her irritability is no longer a factor. Hamilton Score on review is eight.

Discussion

Therapy for acne has become increasingly sophisticated over the years, and along with the advances in sebosuppression have come the hazards of therapy.[1-4] The association between retinoid therapy and teratogenesis has long been noted and forms the basis of protocols for the administration of retinoids.

The other side-effects are less well known, however, and the potential effects on the nervous system are of interest to psychiatrists as they may affect mood, and general functioning, and as indicated in these cases, this mood disturbance can be sufficiently severe as to threaten life. The mode of action of the retinoid class of compounds is unclear, and although the compounds are related to Vitamin A in structure, the side- effect profile may either mimic that seen in hypervitaminosis A or hypovitaminosis A and as the features of these two conditions are very different this is difficult to explain. Vitamin A is known to be essential for retinal function, and this explains the occasional complaint of visual disturbance and colour vision changes made by patients receiving retinoids.[1] The commonly held belief that the side-effects of systemic retinoids are related to a reproduction of the symptoms of the hypervitaminosis A syndrome is now no longer held to be true, as the metabolites of the three oral retinoid preparations, etretinate, acitretin and isotretinoin do not have the same effects as retinoic acid,[5] and, in fact it has been suggested that the effects of isotretinoin are distinctly different from the other two retinoid agents used in dermatological practice. The side effects described in association with retinoid therapy have more in common with the deficiency state of vitamin A, in some instances. The signs of hypervitaminosis A are, irritability, headache, fatigue, myalgia, vomiting, and dry skin, and later, signs of raised intracranial pressure may appear, and in the deficiency state, nyctalopia (night blindness), keratomalacia, dry skin, respiratory infections, and defective spermatogenies[5] and foetal abnormalities have been noted in animals.[10] Thus the spectrum of effects is similar to those described in association with retinoids, where irritability, visual disturbances, dry skin, myalgia and teratogenicity have all been noted[5].

Scheinman *et al*,[8] have observed depressive symptoms in seven patients out of a total of 700 treated with isotretinoin, and they have suggested that the depressive symptoms subside within a week of withdrawal of the compound, and are therefore mild in nature. Other authors have described more catastrophic events in association with the use of retinoids, Bravard *et al*[11] have described parasuicidal acts and completed suicide in association with isotretinoin therapy, and Gatti and Serri,[12] have described the case of a patient who committed suicide some months after a course of treatment with this agent.

These details make harrowing reading, but other authors have suggested that the association between isotretinoin and depression and suicidality is unlikely to be causal,[13] attributing the suicidal behaviour to unrealistic expectations of life without acne, and this argument is strengthened to some extent by the findings of Macdonald Hull and his colleagues,[14] who have suggested that isotretinoin is a useful treatment in the management of depressed acne patients. However, the latter paper dealt with a specific dysmorphophobic subset of acne sufferers. Goulden *et al*, have signalled very clearly their belief that the incidence of depression is very low in those treated with isotretinoin, but their findings are open to alternative interpretation, as persistent lethargy was noted in two of their patients and these patients were lost to follow-up. Obviously these individuals might well have developed

depression, but the outcome in their cases was not determined.[15] Three other patients in Goulden *et al*'s study[15] were noted to experience depressive symptoms but the authors repeatedly suggest that the presence of dysmorphophobia in these individuals in some way minimises the depression diagnosis and they conclude that it is not a long-term side-effect of isotretinoin therapy. An incidence of 0.5%-1% of a sample developing depression, with or without dysmorphophobia, must be seen as significant at a clinical level.

Conclusions

While considerable debate surrounds the nature of the association between retinoid therapy and depression, and the potential for suicide, in the three cases described above the severity of the depressive symptoms was sufficient to necessitate the withdrawal of the treatment in two cases, and active treatment of the depression was required in all three. The continuing depressive symptoms in Case 3 during her continued use of the drug, with the subsequent response to antidepressants following withdrawal of isotretinoin adds further weight to these observations. In view of the concerns regarding the potential of these compounds to produce depression, further research is required to allow this association to be fully evaluated. As is suggested in the cases outlined above, the onset of the depressive symptoms may be extremely variable,[9] and as these individuals would be unlikely to present to dermatologists with complaints of depression, the association between their depressive symptoms and acne therapy might not be readily apparent. Indeed, when later presenting for psychiatric assessment mention might not be made of treatment with isotretinoin as the course of treatment could well have been completed several months prior to the consultation.

The exact mechanism [illegible] isotretinoin is unknown, as is its mode of action in the genesis of irritability and depression. Further studies on the effects of these agents on mood are definitely required. Certain media attention has been drawn to the potential for isotretinoin therapy to produce long-term side-effects, the cases of 21 Norwegian patients have been especially noted,[15] but opinions in this area differ considerably with dermatologists tending to question any adverse effect. Notably, the reported cases of suicide and parasuicide in association with isotretinoin therapy to date have been in younger individuals, and it may well be that young patients require more careful assessment of mental state when receiving retinoids systemically.

References

1. Ginsberg H, Rubenstein A, Brown WV. Medical complications of isotretinoin. Clin Dermatol 1986; 4(1): 183-9.
2. Bonnetblanc JM, Hugon AJ, Dumas M. Intracranial hypertension with etretinate. Lancet 1983; ii: 974.
3. Marsden JR. Lipid metabolism and retinoid therapy. Pharmacol Ther 1975; 40: 55-65.
4. Roenigk HH Jr. Liver toxicity of retinoid therapy. J Am Acad Dermatol 1988; 19: 199-208.
5. Melvor A. Fatal toxic epidermal necrolysis associated with etretinate. BMJ 1992; 304: 548.
6. David M, Hodak E, Lowe N. Adverse effects of retinoids. Medical Toxicology 1988; 3: 273-88.
7. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960; 23: 56-62.
8. Scheineman PL, Peck GL, Rubinow DR, DiGiovanna JJ. Acute depression from isotretinoin. J Am Acad Derm 1990; 1112-4.
9. Saurat H. Side-effects of systemic retinoids and their clinical management. J Am Acad Derm 1992; 27: S23-S28.
10. Mandell HG. Fat soluble vitamins. In: Goodman LS and Gilman A, eds. The Pharmacological Basis of Therapeutics. New York: MacMillan, 1975: 1570-7.
11. Bravard P, Krug M, Rzeznick JC. Isotretinoin et depression, soyons vigilantes. Nouveau Dermatologie 1993; 12: 215.
12. Gatti S, Serri F. Acute depression from isotretinoin. J Am Acad Derm 1991; 25: 132.
13. Peck GL, DiGiovanna JJ, Rubinow DR. Acute depression from isotretinoin, reply. J Am Acad Derm 1991; 25: 132.
14. MacDonald Hull S, Cunliffe WJ, Hughes BR. Treatment of the depressed and dysmorphophobic acne patient. Clinical and Experimental Dermatology 1991; 16: 210-11.
15. Goulden V, Layton AM, and Cunliffe, WJ. Long-term treatment with isotretinoin as a treatment for acne vulgaris. Br J Derm 1994; 131: 360-3.