Experience with St John’s Wort (Hypericum perforatum) in Children under 12 Years with Symptoms of Depression and Psychovegetative Disturbances

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The value of an extract of Hypericum perforatum (St John’s wort) for children with mild to moderate depressive symptoms was investigated for the first time in a multi-centre post-marketing surveillance study. One hundred and one children under 12 years were treated for a minimum of 4 weeks with an extension to 6 weeks with parental consent and medical practitioner recommendation. The dosage used ranged from 300 to 1800 mg per day. Compliance, tolerability and efficacy were assessed every 2 weeks by physicians and parents. Based on the data available for analysis, the number of physicians rating effectiveness as ‘good’ or ‘excellent’ was 72% after 2 weeks, 97% after 4 weeks and 100% after 6 weeks. The ratings by parents were very similar. There was, however, an increasing amount of missing data at each assessment point with the final evaluation including only 76% of the initial sample. Tolerability was good and no adverse events were reported. The results of this study suggest that Hypericum is a potentially safe and effective treatment for children with symptoms of depression. Copyright © 2001 John Wiley & Sons, Ltd.

Keywords: St John’s Wort; hypericum; children; depression; psychovegetative.

INTRODUCTION

Depression is a common disorder in adults and although there are a number of efficacious antidepressant drugs available, they are all burdened by multiple adverse effects. Extracts of Hypericum perforatum (St John’s Wort) have been investigated as an alternative treatment to conventional pharmacological agents and a meta-analysis of 23 randomized controlled trials produced promising results with mild to moderate depressive disorders (Linde et al., 1996). Furthermore, with regard to adverse effects, Hypericum preparations were shown to have an advantage over other antidepressant drugs. The mechanism of action remains unclear, even though at least ten clearly defined compounds have been isolated from Hypericum perforatum extracts, such as flavonoids, biflavonoids, xanthones and naphthodianthrones. To date, synaptosomal uptake or inhibition of serotonin, noradrenaline, dopamine and gammaaminobutyric acid (GABA) as well as down-regulation of noradrenergic β-receptors and up-regulation of 5-HT12 receptors are the most robust findings (Nathan, 1999). In other publications a direct interaction with 5-HT1-receptors (serotonin) has been suggested (Perovic and Müller, 1995). To our knowledge Hypericum extracts have so far only been investigated in adults, so the efficacy and safety of Hypericum perforatum in children is unknown. This post-marketing surveillance study was conducted therefore to investigate whether Hypericum could represent an effective and well-tolerated treatment for children with symptoms of depression.

METHOD

The study was conducted in 35 paediatric outpatient centres between March and November 1998. Children between the ages of 1 and 12 years with symptoms of depression and psychovegetative disturbances were included in the study. The median age was 9 years and the male/female ratio was 64/37. The study lasted 4 weeks but extended to 6 weeks through parental consent and medical practitioner recommendation with one scheduled visit every fortnight. A questionnaire was completed independently by physicians and parents to assess the efficacy and tolerability of treatment. An assessment of overall efficacy was made using the terms ‘worsened’, ‘unchanged’, ‘good’ and ‘excellent’. In addition, the presence of four general symptoms (‘depression’, ‘psychovegetative disturbances’, ‘anxiety’, ‘restlessness’) and eight specific symptoms (‘listlessness’, ‘exhaustion’, ‘irritability’, ‘sleep disturbance’, ‘nervousness’, ‘concentration disturbance’, ‘dejection’,...
‘lack of drive’) were recorded, with the specific symptoms rated as ‘mild’, ‘moderate’, ‘severe’ or ‘not present’. Tolerability was rated as ‘poor’, ‘satisfactory’, ‘good’ or ‘excellent’. Adverse events were recorded. The dosing of the medication was at the discretion of the physician with one coated tablet containing 300 mg *Hypericum perforatum* extract (LI 160 Lichtwer Pharma) standardized to 900 μg hypericin. Parents and physicians were also asked to rate the compliance with the therapy regime as ‘good’, ‘moderate’ or ‘poor’. Since only nominal and ordinal data were collected, the analysis was based on descriptive statistics only.

**RESULTS**

The dose of *Hypericum* administered was at the discretion of the individual physician with the aim being an optimal effect with as low a dose as possible. The median dose was 300 mg/day. Fifteen patients received 300 mg, 26 were administered 600 mg and 25 received 300 mg daily. Three patients were administered the maximum dose of 900 mg daily. In 16 patients the initial dose was reduced, while in seven patients it was increased. No information on dosage was available for the remaining patients. Compliance was rated as ‘good’ for all of the 74 participants for whom compliance ratings were available at the end of the study.

Nine participants discontinued treatment before the end of week 4. In one case this was due to ‘achievement of therapeutic goal’. Six cases were to inadequate therapeutic effect. The other withdrawals were due to difficulty swallowing tablets and going on holiday.

Tolerability ratings were very encouraging with a high degree of concordance between physicians and parents. Based on the data available, the number rating tolerability as ‘good’ or ‘excellent’ was 98% after 2 weeks and 100% after 4 and 6 weeks. There was a decline in the amount of data available for analysis over the 6 weeks assessment period meaning that results were based on 97% of the initial sample at week 2, 90% at week 4 and 75% at week 6.

On the overall efficacy assessment, the numbers of ratings of ‘good’ or ‘excellent’ by physicians were 72% after 2 weeks, 97% after 4 weeks and 100% after 6 weeks based on the data available for analysis. The ratings by parents were similar: 65% after 2 weeks, 93% after 4 weeks and 98% at 6 weeks. However, the amount of missing data also increased at each assessment point with results based on 94% of the initial sample at 2 weeks, 89% after 4 weeks and 76% at the final assessment (Figs 1, 2).

There was a higher turnout of data for the assessment of symptom change with a minimum of 93% of data available for evaluation. The numbers of patients presenting with the four general symptoms were as follows: 47% with ‘depression’, 47% with ‘psychovisitadores disturbances’, 48% with ‘anxiety’ and 54% with ‘restlessness’.

Figure 3 shows the numbers of participants in whom each of the eight specific symptoms was present at baseline. Based on the pre and post-treatment ratings, each one was categorized as ‘worsened’, ‘unchanged’, ‘improved’ or ‘cured’.

**Figure 1.** Physician’s assessment of efficacy (%) after 4 weeks treatment.

**Figure 2.** Physician’s assessment of efficacy (%) after two weeks and at the end of extended treatment to 6 weeks respectively.
Only one case of worsening symptoms was recorded throughout the total study course. This was for ‘nervousness’ which changed from ‘not present’ at baseline to ‘mild’ at 2 weeks. It subsequently disappeared. Assessments of ‘unchanged’ symptoms were only made in cases where baseline symptoms were ‘mild’. For all ‘moderate’ or ‘severe’ symptoms an ‘improvement’ or ‘cure’ was reported. Figure 4 shows the proportions of participants ‘cured’, ‘improved’ and ‘unchanged’ for each symptom at the end of the study.

The proportions of participants judged to be ‘cured’ after the 6 week treatment period are presented in Table 1 for each of the specific depressive symptoms. The ‘cure’ rate is shown separately for those classified as ‘mild’, ‘moderate’ or ‘severe’ at baseline. Apart from ‘lack of drive’ (44%) all the symptoms were diagnosed in well

### Table 1. Percentage of participants judged to be ‘cured’ at 6 weeks listed according to baseline assessment of symptom severity

<table>
<thead>
<tr>
<th>Presenting symptom (% of sample)</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of drive (44%)</td>
<td>96%</td>
<td>89%</td>
<td>80%</td>
</tr>
<tr>
<td>Dejection (61%)</td>
<td>100%</td>
<td>89%</td>
<td>67%</td>
</tr>
<tr>
<td>Concentration disturbances (90%)</td>
<td>58%</td>
<td>66%</td>
<td>34%</td>
</tr>
<tr>
<td>Nervousness (82%)</td>
<td>95%</td>
<td>35%</td>
<td>45%</td>
</tr>
<tr>
<td>Sleep disturbances (75%)</td>
<td>90%</td>
<td>91%</td>
<td>92%</td>
</tr>
<tr>
<td>Irritability (72%)</td>
<td>62%</td>
<td>85%</td>
<td>57%</td>
</tr>
<tr>
<td>Exhaustion (59%)</td>
<td>92%</td>
<td>90%</td>
<td>75%</td>
</tr>
<tr>
<td>Listlessness (64%)</td>
<td>92%</td>
<td>89%</td>
<td>75%</td>
</tr>
</tbody>
</table>
over half the sample with ‘concentration disturbances’ being the most frequent at 90%. This symptom was also the most resistant to treatment, although over half of those in whom it was ‘mild’ or ‘moderate’ and over a third of ‘severely’ affected children, were ‘cured’ by 6 weeks. For most symptoms, over 90% of participants in the ‘mild’ category, over 85% of those ‘moderately’ affected and over half of those classified as ‘severe’ were ‘cured’. ‘Sleep disturbances’ were ‘cured’ in over 90% of affected and over half of those classified as ‘severe’ were in the ‘mild’ category, over 85% of those ‘moderately’ affected and over half of those classified as ‘severe’ were ‘cured’. ‘Sleep disturbances’ were ‘cured’ in over 90% of participants from all categories.

Discussion

The results of this study suggest that the Hypericum perforatum extract LI 160 is a potentially effective treatment strategy for children under 12 years with symptoms related to depression and psychovegetative disorders.

Assessments of compliance and tolerability were very encouraging. Although no adverse events were reported in this study, it is possible that some went undetected. Children treated with Hypericum extracts should be carefully monitored for adverse events that have been reported in trials involving adult patients such as gastric discomfort, loss of appetite, dizziness or allergic reactions (Woolk et al., 1994).

Since no standardized measure is available for the assessment of depression in children, a questionnaire was used in this study to document the course of 12 typical symptoms. There was good concordance between the assessments by physicians and parents and high correlation between ratings of overlapping symptoms such as restlessness, nervousness and irritability.

For all symptoms, there was evidence of a clear beneficial effect. This has been demonstrated in a number of clinical trials with adult patients (Vorbach et al., 1997; Wheatley, 1997; Volz, 1997), but this is the first study to investigate the use of Hypericum perforatum in children. The results suggest that Hypericum may prove to be a safe and effective treatment option for children under 12 years with depression and psychovegetative disorders.

References


