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Is Clofibrate (Atromid-S) a Safe and Effective Adjunctive Treatment to Phototherapy for Neonatal Jaundice?

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Is clofibrate (Atromid-S) a safe and effective adjunctive treatment to phototherapy for neonatal jaundice?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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In
Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

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Abstract

Objective: To determine, “Is clofibrate a safe and effective adjunctive treatment to phototherapy for neonatal jaundice?”

Study Design: Review of three English language, randomized controlled trials (one of which was double-blind) published between 2005-2009.

Data sources: Randomized controlled clinical trials comparing a one-time oral dose of clofibrate (100 mg/kg) plus phototherapy compared to phototherapy alone were found using Cochrane and EBSCOhost.

Outcomes Measured: The outcomes in all three studies were duration of phototherapy (measured in hours) and the safety of clofibrate (measured by the report of side effects at follow-up).

Results: All three trials demonstrated that the one-time dose of oral clofibrate (100 mg/kg) in addition to phototherapy significantly decreases the duration of phototherapy needed for the treatment of neonatal jaundice. Follow-up arrangements were made for two days, one week and one month for the Mohammadzadeh, Sakha, and Badeli trials respectively. Two studies had no reported side effects noted at follow-up, but the Sakha trial noted an episode of rebound increases in bilirubin levels in an infant in the control group.

Conclusions: Clofibrate is an effective adjunctive treatment when combined with phototherapy for treatment of neonatal jaundice. However, longer follow-up studies are needed to determine the true safety of the drug and the incidence of any long-term sequelae.

Key Words: clofibrate, Atromid-S, neonatal jaundice.
Introduction

Neonatal jaundice is a common problem among newborns. In fact, up to 60% of full-term and 80% of pre-term newborns worldwide are diagnosed with jaundice within the first seven days of life. The term ‘jaundice’ is generally characterized by a visible “yellowing” of the skin. Once jaundice is noted in an infant, the severity of the condition is then determined by a blood test (total serum bilirubin) to determine if treatment is necessary. Bilirubin is an end-product of red cell breakdown in the body (this is called ‘indirect’ bilirubin). In a normal infant, the ‘indirect’ bilirubin in the blood is converted into ‘direct’ bilirubin in the liver. Direct bilirubin is then excreted in the stool via the gut. However, when the ‘indirect’ bilirubin is not efficiently converted into ‘direct’ bilirubin it accumulates in the body leading to the “yellow” color characteristic of jaundice. Although many cases of newborn jaundice do not cause permanent damage, severe cases that are not treated quickly can lead to a brain damage referred to as, “kernicterus” which can lead to life-long complications.

The cost to treat neonatal jaundice can vary greatly from one infant to another depending on the severity of the condition. For those with mild jaundice, the practitioner may choose to check the infant a couple times per week in the office to ensure the issue is resolving. In moderate to severe cases, it is likely that the newborn will need to be treated with phototherapy. For those newborns whose condition requires in-patient treatment, it is likely that an extensive hospital bill will accrue due to phototherapy machines, monitors, and tests essential for tracking the condition.

The high incidence of neonatal jaundice explains how important this condition is to practitioners. Physician assistants in family medicine, pediatrics, emergency medicine and
internal medicine are likely to be exposed to cases of neonatal jaundice during their career. In addition, it is critical that practitioners have an understanding of the available treatments for neonatal jaundice, as this disease can be time-critical if the condition is severe.

Currently, the mainstay of treatment of neonatal jaundice is phototherapy where the infant is put in an incubator and exposed to lights, which helps the body excrete the excess bilirubin into the stool. This form of therapy is effective, however, improvement takes days and can lead to dangerous side effects such as retinal damage, hyperthermia (or increased body temperature), and diarrhea.¹ Although precautions are taken to ensure that side effects are minimal (such as covering the infants eyes during treatment) there is still a possibility of danger. In severe cases of neonatal jaundice, an exchange transfusion (remove blood and related products from the body and replace them with products from a donor) may be indicated to help prevent kernicterus.³ Other possible interventions include medications such as Phenobarbital, D-penicillamine, and oral charcoal, but these treatments are not widely used and are still being researched for efficacy.¹ Clofibrate (brand name Atromid-S) is another drug treatment being researched, but it is not considered an alternative to phototherapy. Instead, it is thought that by adding a single dose of oral clofibrate (100 mg/kg) to the phototherapy treatment the duration of phototherapy needed would be decreased (because clofibrate helps indirect bilirubin convert to direct bilirubin).²

Objective

The objective of this limited systematic review is to determine, “Is clofibrate a safe and effective adjunctive treatment to phototherapy for neonatal jaundice?”
Method

A thorough search was conducted by the author using the Cochrane Database of Systematic Reviews and Clinical Trials as well as EBSCOhost. All studies were published in English, located in peer-reviewed journals, and dated between 2005-2009. The key words used to search for studies were “clofibrate,” “Atromid-S,” and “neonatal jaundice.” The three studies utilized for this limited systematic review included newborns born either at term (38-41 weeks) or late pre-term (34-37 weeks) diagnosed with neonatal jaundice and admitted to the hospital (specifically those with a serum bilirubin between 15-29.9 mg/dl). The studies all used the same intervention of a single dose of oral clofibrate 100 mg/kg as an adjunct to phototherapy. These intervention groups were compared to control groups, which only received phototherapy. The main outcomes measured were the effect on jaundice (measured by duration of phototherapy) and the safety of clofibrate (measured by reported side effects). Both of the outcomes measured are patient oriented evidence that matters (POEM). All of the studies were randomized controlled trials (one of which was double-blind).

The inclusion criteria for the studies were as follows: born at term (38-41 weeks) or late pre-term (34-37 weeks), breastfed, serum bilirubin between 15-29.9 mg/dl, and body weight between 2500-4000g. The exclusion criteria for the studies were as follows: congenital abnormalities, G6PD deficiency, infection, dehydration, and hemolytic disorders (such as ABO or Rh incompatibility). Table 1 includes the demographics for the studies utilized. Statistics reported include p-values with confidence intervals (CI), numbers needed to treat (NNT), relative risk reduction (RRR), absolute risk reduction (ARR).
### Results: Table of demographics of included studies (Table 1)

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th># Pts</th>
<th>Age (years)</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>W/D</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Badeli, Iran</td>
<td>RCT</td>
<td>90</td>
<td>38-41 weeks</td>
<td>breastfed, serum bilirubin between 15-29.9 mg/dl; body wt between 2500-4000g</td>
<td>dehydration; infection; ABO or Rh incompatibility; G6PD deficiency; conjugated bilirubin &gt;15% of total serum bilirubin; congenital anomalies</td>
<td>0</td>
<td>phototherapy VS. phototherapy + clofibrate (100 mg/kg x1 dose)</td>
</tr>
<tr>
<td>Mohammadzadeh, India</td>
<td>RCT</td>
<td>60</td>
<td>38-41 weeks</td>
<td>breastfed; serum bilirubin 17-29.9 mg/dl; healthy</td>
<td>congenital anomalies; hemolytic disease; infection; dehydration; G6PD deficiency; conjugated bilirubin &gt;15% of total serum bilirubin</td>
<td>0</td>
<td>phototherapy VS. phototherapy + clofibrate (100 mg/kg x1 dose)</td>
</tr>
<tr>
<td>Sakha, India</td>
<td>Double-blind RCT</td>
<td>68</td>
<td>34-37 weeks</td>
<td>non-hemolytic jaundice; no need for exchange transfusion</td>
<td>congenital anomalies; hemolytic disorders; G6PD deficiency; sepsis or significant accompanying illness</td>
<td>0</td>
<td>phototherapy VS. phototherapy + clofibrate (100 mg/kg x1 dose)</td>
</tr>
</tbody>
</table>

### Outcomes Measured

The primary outcomes measured in all three studies were duration of phototherapy (measured in hours) and the safety of clofibrate, both of which are POEMs. The safety of clofibrate was measured by the side effects reported by parents at follow-up after the infant was discharged home.

### Results

The results pertaining to the duration of phototherapy were presented in continuous data as hours of phototherapy endured by the patients. The data was then presented in the articles as a mean number of hours of phototherapy needed with the standard deviations (SD) also included (Table 2). For ease of communication, this limited systematic review will refer to the study
Results: Efficacy of Clofibrate + Phototherapy on Duration of Phototherapy (Table 2)

<table>
<thead>
<tr>
<th></th>
<th>Clofibrate</th>
<th>Control</th>
<th>Clofibrate</th>
<th>Control</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Badelli, 2008</td>
<td>38.8 +/- 7.5</td>
<td>68.75 +/- 15.4</td>
<td>20-48</td>
<td>36-96</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mohammadzadeh, 2005</td>
<td>30 +/- 12.89</td>
<td>54 +/- 18.83</td>
<td>12-48.</td>
<td>24-96</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Sakha, 2009</td>
<td>64.32 +/- 12.48</td>
<td>87.84 +/- 29.76</td>
<td>CI= 60-81.6</td>
<td>CI= 79.2-108</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

SD= standard deviation; CI= confidence interval

groups as control (phototherapy only) or clofibrate (phototherapy + 100 mg/kg of clofibrate x1 dose). For the Badelli, 2008 study the infants in the clofibrate group needed an average of 38.8 hours (SD=7.5; range 20-48) of phototherapy while the control group required 68.75 hours (SD=15.4; range 36-96), which was a significant difference (p<0.001). The Mohammadzadeh, 2005 study also had a significant difference in phototherapy duration (p<0.0001); the clofibrate group requiring a mean of 30 hours (SD=12.89; range 12-48) and the control group 54 hours (SD=18.83; range 24-96). The newborns in the Sakha, 2009 clofibrate group received an average of 64.32 hours (SD=12.48; CI=60-81.6), while the control received 87.84 (SD=29.76; CI=79.2-108); this finding is significant (p<0.001).

The results for the incidence of side effects are summarized in Table 3. For both the Badelli, 2008 and the Mohammadzadeh, 2005 studies there were no adverse effects reported at follow-up for any of the participants regardless of the group they were in (control versus clofibrate). However, the Sakha, 2009 trial had one incidence of rebound increases in bilirubin levels (called rebound hyperbilirubinemia); the patient was a member of the control group. The RRR and ARR were calculated to be 1% and 0.03% respectively. Number needed to treat (NNT) was deemed to be -33 with the one-time oral clofibrate dose of 100 mg/kg.
Results: Safety of Clofibrate as measured by side effects (Table 3)

<table>
<thead>
<tr>
<th>Study</th>
<th>% of pts in control group with side effects</th>
<th>% of pts in study group with side effects</th>
<th>RRR</th>
<th>ARR</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Badelli, 2008</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mohammadzadeh, 2005</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sakha, 2009</td>
<td>0.03%</td>
<td>0</td>
<td>-1%</td>
<td>-0.03%</td>
<td>-33*</td>
</tr>
</tbody>
</table>

SE= side effects; RRR= relative risk reduction; ARR= absolute risk reduction; NNT= numbers needed to treat

* Since the outcome measured here is the incidence of side effects, the negative NNT means that for every 33 patients who received clofibrate there was 1 less incidence of reported side effects than those who received phototherapy alone.

Discussion

All three of the studies contained in this limited systematic review demonstrated a significantly lower duration of phototherapy needed for infants who received the one-time dose of clofibrate in addition to phototherapy (clofibrate group) when compared to newborns who received phototherapy alone (control group). In addition, the newborns in the control group required an average of at least twenty-three additional hours of treatment with phototherapy before meeting qualifications for discharge when compared to the clofibrate group. These results show that the hospital stay for newborns requiring treatment for jaundice can be decreased by a minimum of one day by simply adding a one-time dose of clofibrate.

The studies also seem to indicate that clofibrate is a safe drug to use in infants. Each study arranged a follow-up appointment to determine if parents noted any side effects. The Mohammadzdeh, 2005 study had the quickest follow-up at 2 days, while the Sakha, 2009 and Badeli, 2008 studies followed up at one week and one month respectively. Although there were no reports of side effects at follow-up, it is not enough to deem the use of clofibrate safe due to the history of the drug.
Clofibrate was originally used to treat high cholesterol and was taken at a dose of 500 mg per day by adults. However, after studies demonstrated an increased mortality rate during active use of the drug in the 1980’s, its production was discontinued in the United States. In spite of this, studies also indicated mortality rates decrease significantly after termination of use. Therefore, it is possible that the use of clofibrate may be completely safe for use in the treatment of neonatal jaundice as it is only a one-time dose and not a continuing medication regimen. Nevertheless, the studies in this limited systematic review did not follow-up nearly long enough to rule out long-term sequelae, which makes this a huge limitation to these studies.

Another limitation is the fact that each study used a different technique of administering phototherapy. The Sakha, 2009 trial utilized units containing eight blue fluorescent tubes situated at 20-cm above the infant. The Mohammadzadeh, 2005 trial also situated the lights 20-cm above the infant, but used six white lamps instead of the blue used in the Sakha, 2009 trial. Finally, the Badeli, 2008 trial used four white lights positioned 30-cm above the newborn. Although the results in each trial demonstrated a decreased phototherapy time with clofibrate, the results would be more convincing with the same phototherapy technique used among the studies. In addition, it is possible that the difference in lights may have had an effect on the outcome of the studies.

Conclusion

Clofibrate is an effective adjunctive treatment when combined with phototherapy for treatment of neonatal jaundice. However, longer follow-up on patients and further research on long-term effects of the drug on the infant is needed to get this drug approved by the FDA for use in the United States.
References


2. Clofibrate Supplier | [CAS 637-07-0] | Tocris Bioscience


