Journal of Clinical Pharmacy and Therapeutics (2005) **30**, 291–295

ORIGINAL ARTICLE

Proposed mechanisms and preventative options of Jarisch–Herxheimer reactions

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SUMMARY

Objective: **To review the aetiologies and preventative methods associated with Jarisch–Herxheimer reactions (JHR).**

Data sources: **Ovid Medline® (1966–June Week 1 2004) was utilized to assess biomedical literature; a review of the bibliographies of articles was also performed.**

Data synthesis: **JHR often occurs with the treatment of spirochete infections. However, the mechanism by which the reaction takes place is not clearly defined.**

Conclusion: **Studies suggest with conflicting evidence that the JHR is caused by release of endotoxin-like material from the spirochete as well as cytokine elevation in the body. It appears the type of drug and the rate of spirochete clearance from the body have little effect on the incidence of the reaction. Many pretreatment options have been explored with limited efficacy with the exception of anti-tumour necrosis factor antibodies.**

***Keywords*: antibiotics, cytokines, endotoxin, Jarisch–Herxheimer reactions, spirochete**

INTRODUCTION

The Jarisch–Herxheimer Reaction (JHR) was originally described in 1895 by Jarisch and 7 years later by Herxheimer and Krause. They each separately described a reaction that occurred in patients with syphilis who were treated with mercury (1, 2). Since that time, the JHR has been associated with the antimicrobial treatment of spirochete infections and has been observed in syphilis (3, 4), leptospirosis (5), lyme disease (6), tick-borne relapsing fever (7) and louse-borne relapsing fever (8). The reaction has been reported to occur in 75–80% of those treated for syphilis, 54% of those treated for tick-borne relapsing fever and 82% of those treated for louse-borne relapsing fever (7, 9–11). The reaction typically occurs within a few hours after the initiation of antimicrobial treatment for the disease and often presents with the following symptoms: headache, fever, rigours, malaise, hypotension and sweating. The symptoms of the presenting disease may also worsen (4, 12). These symptoms often resolve without intervention within 12–24 h (3, 4). In syphilis, the severity of the JHR appears to be related to the stage of the disease and is more severe and may even be fatal in primary and early secondary syphilis as compared with late tertiary syphilis (4). The JHR is known to occur as an 'all or none' principle that is determined by a certain unknown number of spirochetes. If that specific number is not reached, the reaction will not occur (3). Mechanisms of how this reaction develops are not completely understood; proposed mechanisms and preventative strategies will be reviewed.

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LITERATURE REVIEW

The prevailing theory surrounding the aetiology of the JHR implicates endotoxin as the precipitating factor (8–10, 13–16). The endotoxins in question are the lipoproteins released from *Treponema pallidum* and *Borrelia* spp. (16). In most of the studies examining the JHR, the presence or absence of endotoxin was determined using the limulus assay. This assay is typically used to show the presence of endotoxin in the blood associated with

Gram-negative bacteraemia. There is considerable variability among the various studies in their ability to detect endotoxin. In these studies, the limits of detection ranged from 0·01 to 50 ng/mL using the standard comparative endotoxins from *Escherichia coli* and *Klebsiella* spp. (9, 10, 13–16). Two studies support the role of endotoxin or treponemal lipopolysaccharide with the JHR by positive test results with the limulus assays (positive detection at 0·1 ng/mL for both studies) (9, 13). Although the JHR has not been reported with Gram-negative bacterial infections, the endotoxin associated with JHR in these studies may have been altered or the specificity of the limulus assay may be in question (17, 18). Other studies have failed to detect the presence of endotoxin with the JHR utilizing the same testing methodology (10, 14–16). The conflicting results of these studies may be due to the different quantities of spirochete yields obtained as well as the various detection limits utilized; thus, the sensitivity of the assay may have been low, and therefore the ability to detect a small amount of endotoxin may have been compromised, yielding a false-negative result.

Another proposed aetiologic theory of the JHR involves the transient elevation of cytokines released as a result of drug treatment. Although cytokines are usually associated with an inflammatory process, it has been demonstrated in two studies that tumour-necrosis factor (TNF), interleukin-6 (IL-6) and IL-8 are involved with the JHR, each peaking at different times throughout the reaction; TNF elevates first, shortly after antibiotic administration, followed by IL-6 at the onset of symptoms and finally IL-8. It is concluded from these studies that symptoms of the JHR are strongly associated with these cytokine elevations (11, 19).

The choice of antibiotics in the treatment of these spirochete infections has also been targeted as the cause of the JHR. A study by Nadelman *et al.* (20) found that the more rapid bactericidal effect of the beta-lactam drug, cefuroxime, may lead to a higher incidence of the JHR compared with the bacteriostatic drug, doxycycline, in the treatment of early lyme disease. In this blinded, randomized study ($n = 123$), 29% of those treated with cefuroxime developed the JHR compared with only 8% of those treated with doxycycline ($P = 0·005$) (20). On the other hand, an earlier study by Butler *et al.* (21) demonstrated that the bacteriostatic drug is associated with a higher incidence of the JHR; in this study, contrary to the previous one, 15 of 15 patients taking tetracycline developed rigours while only 10 of 15 penicillin G patients experienced rigours. Other statistically significant differences noted favouring tetracycline include time to maximum temperature, defervescence and onset of rigours (21). A similar treatment regimen [oral tetracycline (250 mg for age ≤12 years of age and 500 mg for adults) vs. intramuscular (i.m.) procaine penicillin (200 000 U for ≤12 years of age and 600 000 units for adults)] was also studied in louse-borne relapsing fever patients ($n = 120$). The incidence of the JHR was similar in both treatment groups (45% in the tetracycline group as opposed to 35% in the penicillin group, $P > 0·05$), although the reaction was more prolonged in the penicillin group (20·1 h vs. 8·4 h, tetracycline group, no *P*-value stated) (22).

Another proposed theory of the JHR involves the rate of spirochete clearance. Warrell *et al.* (23) found that patients treated with slow-release i.m. procaine penicillin and aluminium monostearate had the same incidence of the JHR (100%) compared with tetracycline-treated (i.v.) patients with louse-borne relapsing fever with confirmed *Borrelia* spirochetemia ($n = 12$). However, the spirochete was cleared more rapidly with the administration of tetracycline (<5 h in the tetracycline group compared with >25 h in the penicillin group). These results mirror two previously discussed studies by Gebrehiwot *et al.* and Butler *et al.* (21, 22). Based on the results of these trials, the spirochete appears to be eradicated more rapidly from the blood with the use of a tetracycline-type antibiotic as compared with a beta-lactam drug (21–23). Two of these studies showed favourable response and complete recovery in both treatment groups, although Gebrehiwot *et al.* reported four treatment relapses in the penicillin group compared with no treatment relapses in the tetracycline. While it may be beneficial regarding spirochete clearance to use a tetracycline product, the incidence of the JHR and even clinical efficacy of the treatments in the studies were conflicting.

Several studies have examined the prevention of the JHR by targeting cytokine production (12, 24). Fekade *et al.* (12) studied 49 patients with *Borrelia recurrentis* spirochete infection; 20 patients were

pretreated with sheep TNF-α antibodies (120 mg total Fab/kg body weight) immediately prior to antibiotic administration to prevent the JHR with penicillin (600 000 U) therapy while the other 29 patients served as the control group. The JHR was reported as absent to severe, with absent referring to no shaking and severe referring to continued rigours. A significantly higher number of patients in the control group developed JHR compared with the pretreatment group (90% vs. 50%, $P = 0{\cdot}0006$). In addition, the severity of the JHR in the TNF antibody group was also lessened (only mild compared with 48% having moderate to severe reactions in the control group). It was concluded from this trial that anti-TNF-α does appear to reduce both the incidence and severity of the JHR associated with penicillin treatment for louse-borne diseases (12).

Interleukin-10, a potent inhibitor of the secretion of inflammatory cytokines, has also been evaluated as a preventative measure for the JHR. In a randomized, double-blind, placebo-controlled study (24), 49 patients with *B. recurrentis* infections were randomized to receive either 25 μg/kg of recombinant human IL-10 or placebo prior to receiving i.m. penicillin (600 000 U). Endpoints included physiologic changes, rate of spirochete clearance and plasma cytokine levels. The incidence of the JHR was similar among the two groups (IL-10 group, 96% and placebo, 100%, $P > 0{\cdot}05$). There were marked increases in cytokine peak levels after treatment in the IL-10 group, although these were not statistically significant (placebo vs. IL-10 groups, respectively, mean values in pg/mL: TNF-α = 200 vs. 368, IL-6 = 77 111 vs. 134 861, IL-8 = 1644 vs. 2267). In addition, there were no statistically significant effects on spirochete clearance from the body (IL-10, 9·9 h vs. placebo, 10·9 h). It is possible that the dose of IL-10 was subtherapeutic to prevent or lessen the JHR or the timing of IL-10 administration was inappropriate. Despite these unknowns, the authors concluded IL-10 had no effect on the prevention of the JHR associated with *B. recurrentis* infections (24).

Pentoxifylline, FDA approved for the treatment of intermittent claudication, has been evaluated for the prevention of the JHR with disappointing results as well (25). In one study, 14 patients with *B. recurrentis* infection received intravenous pentoxifylline (300 mg loading dose, then 40 mg/h for 16 h) 90 min before treatment with penicillin intramuscularly; four patients served as the control group. There was no difference in the incidence of the JHR between groups (100% in both groups). The subjective assessment of the severity of the JHR was also similar among the two groups (pentoxifylline: 29% mild, 71% moderate to severe; control: 25% mild, 75% moderate to severe). In addition, cytokine levels were not reduced with the addition of pentoxifylline (25).

Other attempts have been made to lessen or prevent the JHR. As discussed above, antibodies against certain cytokines (TNF-α) have shown to decrease the incidence of the JHR compared with the control group and to suppress the symptoms of the reaction, including fever, elevated heart rate and systolic hypotension (12). Corticosteroids and acetaminophen have also been evaluated with no effect on the prevention of the JHR (21). In a study of 51 patients with louse-borne relapsing fever, Butler *et al.* (21) randomly assigned 15 patients who received erythromycin to acetaminophen 650 mg by mouth ($n = 5$), hydrocortisone 500 mg intravenously ($n = 5$) 2 h before and 2 h after antibiotic administration. Five patients served as the control group receiving no premedications. The steroid-treated group had a lower body temperature and the JHR was considered shorter in duration as compared with the acetaminophen and control groups; time to defervescence was also shorter in the hydrocortisone group (7·6 h vs. 12·8 h in the acetaminophen group and 11·4 h in the control group). Both intervention groups reported a statistically smaller decrease in systolic blood pressure compared with the control group (acetaminophen: 15 mmHg, hydrocortisone: 17 mmHg, and control: 29 mmHg). Although the JHR may have been lessened, it was not prevented. Possible limitations include the unknown of the exact effective dose as well as timing and schedules of hydrocortisone or acetaminophen. In this study, the interventions were administered only before and after the antibiotic dose; it is unknown whether more doses given either before or after may have been of benefit (21).

Gudjonsson *et al.* (26) also evaluated the utility of a steroid and its effects on the JHR in patients with primary syphilis. In this study, 15 patients, serving as the control group, were given penicillin on days 1 and 2 or 3. Another 17 patients also received the same penicillin regimen as the control

group; in addition, they also were given 20–60 mg of oral prednisolone on the first and second day of antibiotic administration. In this study, the JHR was defined as an increase in body temperature to ≥38 °C as measured rectally. While 93% of the control group developed the JHR, only 12% developed the reaction in the steroid group. The two patients who did become febrile in the steroid group were on 20 and 40 mg of prednisolone each. None of the 60 mg prednisolone patients developed the JHR. Thus, the use of the steroids proved quite beneficial in preventing the febrile effects of the JHR in this study. However, other clinical aspects of the JHR such as blood pressure, rigours and sweating were not evaluated. The evaluation of these symptoms would have provided more evidence towards the overall effects of prednisolone therapy (26).

Another drug, meptazinol, an opioid analgesic with both agonist and antagonist properties, has been shown to lessen the severity of the JHR, but not entirely prevent it (27). Teklu *et al.* (27) randomized 24 patients with louse-borne relapsing fever being treated with intravenous tetracycline in a double-blind fashion to one of three groups: naloxone 10 mg, meptazinol 100 mg or placebo each given by slow intravenous infusion (i) with antibiotic administration, (ii) 30 min after antibiotic administration, and (iii) if the systolic blood pressure decreased <70 mmHg. The JHR incidence among the three groups was 100%. While the use of both naloxone and meptazinol had no effect on the incidence of the JHR, meptazinol shortened the duration of chills (29 min vs. 42 min, naloxone and 45 min, placebo), delayed the associated fever (174 min vs. 114 min, naloxone and 119 min, placebo) and reduced the maximum temperature (40·9 °C vs. 41·7 °C, naloxone and 41·5 °C, placebo). While these were statistically significant ($P < 0{\cdot}05$), the temperature difference and time to fever were not likely clinically significant. There were also fewer alterations in heart rate and respiratory rates in the meptazinol group ($P < 0{\cdot}04$). Although the symptoms were lessened, the JHR was not prevented (27). Unlike some of the previous studies, this trial assessed many aspects of the JHR specifically focusing on the clinical effects. This was the first trial, to our knowledge, assessing the use of meptazinol in the JHR; the dose, duration and frequency of the medication appeared to be efficacious in reducing the symptoms of the JHR.

The use of antihistamines has also been considered in one case report with little effect (28). In this report, a 31-year-old female with secondary syphilis was treated with intramuscular benzathine penicillin G. She did not have a history of a penicillin allergy. Within 4 h after antibiotic administration, she developed fever, headache and arthralgia with vesicular lesions developing on her midsection and extremities. Despite diphenhydramine 25 mg by mouth every 4 h, the lesions did not improve for several days. The exact number of days, unfortunately was not reported (28).

CONCLUSION

Although the JHR was first described over 100 years ago, much is still unknown about it. While many aspects of the JHR have been studied to determine causality as well as preventative measures, much of the data consists of case reports and studies with small sample sizes. It appears the reaction may be the result of both an endotoxin-like substance as well as cytokine elevation. Although difficult to perform, further understanding of the complexity of the JHR will require larger, well-designed studies. Until that time, the exact mechanism behind the JHR will remain unknown, and thus the possible preventative measures will remain a mystery. To date the best evidence from the available randomized, controlled trials in the prevention of the JHR has been with TNF-α antibodies and in some cases, steroids. While other premedications such as acetaminophen and meptazinol may reduce the symptoms or duration of the JHR, the reaction itself is not prevented.

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