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A Proof-of-Concept Trial of Protein Kinase C Iota Inhibition with Auranofin for the Paclitaxel-Induced Acute Pain Syndrome

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Abstract

Purpose—Paclitaxel causes the paclitaxel-induced acute pain (PIAP) syndrome. Based on preclinical data, we hypothesized that the protein kinase C (PKC) iota inhibitor, auranofin (a gold salt used for other pain conditions), palliates this pain.

Methods—In a randomized, double-blinded manner, patients, who had suffered this syndrome, were assigned a one-time dose of auranofin 6 mg orally on day #2 of the chemotherapy cycle (post-paclitaxel) versus placebo. Patients completed the Brief Pain Inventory and a pain diary, on days 2 through 8 and at the end of the cycle. The primary endpoint was pain scores, as calculated by area under the curve, in response to “Please rate your pain by circling the one number that best describes your pain at its worse in the last 24 hours,”

Results—Thirty patients were enrolled. For the primary endpoint, mean area under the curve of 55 units (standard deviation 19) and 61 units (standard deviation 22) were observed in auranofin-treated and placebo-exposed patients, respectively (p=0.44). On day 8 and at the end of the cycle, pain scores in auranofin-treated patients were more favorable, although differences were not statistically significant.

Conclusions—In the dose schedule studied, auranofin did not palliate the PIAP syndrome, but delayed beneficial trends suggest further study for this indication.

Keywords

myalgias; protein kinase C; auranofin

Paclitaxel is a commonly prescribed drug for cancer of the lung, breast, ovary, endometrium, bladder, esophagus, head and neck and other malignancies [1–5]. This agent causes a unique, distressing syndrome: the paclitaxel-induced acute pain (PIAP) syndrome [6–8]. Diffuse, refractory pain that remains unresponsive to even opioids is a seminal feature,

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occurring in 70% of patients who receive paclitaxel at a dose of at least 70 mg/m.^{2} Pain begins within 2–7 days after paclitaxel, but the worst pain occurs on days 3–4 with no clearly defined time of cessation. Patients describe pain in the legs, feet, hips, abdomen, back, arms, shoulders, hands, neck, and chest; and, in 15% of patients, this pain can be severe. Because some paclitaxel regimens are given weekly and because this pain continues for at least one week, patients can suffer from paclitaxel-induced pain almost constantly throughout the chemotherapy cycle. At times, this pain prompts cessation of cancer therapy [9,10].

Here, we explored the hypotheses that the PIAP syndrome is mediated by protein kinase C (PKC) iota and that auranofin, a gold salt and an inhibitor of this enzyme, palliates this syndrome [10–12]. Three lines of evidence provide the rationale for these hypotheses. First, cell line data from our group showed that exposure to paclitaxel results in sustained activation of PKC iota [13]. Increased PKC iota activity was observed at 6 hours, peaked at 12 hours, and continued over the ensuing 36 hours. Second, PKC iota is detectable in muscle, although presumably at levels that do not induce pain in the absence of paclitaxel. In analyzing normal, human skeletal muscle, our group observed expression, thereby adding further credibility to the possibility that PKC iota mediates this syndrome [14]. If paclitaxel-induced pain is emanating from muscle tissue, then it stands to reason that a putative key mediator of this pain would be present in this same body compartment; and it appears to be. Third, it is known that tissue damage releases a host of substances such as prostaglandins, bradykinin, and substance P and that the PKC isoenzymes serve as toggle points for generating increased pain after tissue damage [15–17]. The PKC isoenzymes depolarize unmyelinated afferent neurons and sensitize them to tissue damage. Other pain syndromes in which the PKC isoenzymes have clearly been implicated include chronic diabetes pain, postoperative chronic pain, and pain from burns [16,17]. The possibility that PKC iota might also mediate the PIAP syndrome appears consistent with what has been observed in these other pain syndromes [16–20]. Finally, the agent auranofin – which palliates pain in autoimmune arthritis, improves functionality, and is well-tolerated –inhibits PKC iota [21]. Given the foregoing, we conducted a proof-of-concept study to test the hypothesis that auranofin palliates paclitaxel-induced pain.

METHODS

Overview

This randomized, double-blinded, placebo-controlled trial was conducted at the Mayo Clinic in Rochester, Minnesota with Institutional Review Board (IRB) approval.

Eligibility Criteria

Eligible patients met the following criteria: 1) age >/=18 years; 2) previously experienced paclitaxel-induced pain deemed consistent with the commonly-observed PIAP syndrome, as per the patient's healthcare provider (of note, the protocol provided an in depth characterization of this syndrome [6–8]); 3) scheduled to receive a dose of paclitaxel of >/= 70 mg/m^2 within 14 days of randomization to the current trial; 4) able to complete a symptom questionnaire either independently or with assistance. The following were required

within 14 days of registration: 1) absolute neutrophil count >/= 1.5 x 10^9 cells/L; 2) platelet count >/= 100,000 x 10^9 cells/L; 3) creatinine </= 2 times the upper limit of normal; 4) either the alanine aminotransferase (ALT) or the aspartate aminotransferase (AST) in addition to the total or direct bilirubin and the alkaline phosphatase </= 1.5 times the upper limit of normal; and 5) hemoglobin >/= 9 grams/dl. Women of child-bearing potential had to have had a negative pregnancy test.

Patients were excluded with any of the following: 1) prior gold-induced disorders or gold hypersensitivity; 2) taking phenytoin or another gold-containing compound immediately prior to study entry; 3) anticipated use of granulocyte stimulating factor or granulocyte or monocyte stimulating factor within 30 days because these agents have the potential to cause pain and confound study conclusions; or 4) concurrent immune-modulating agents. Of note, the trial eligibility criteria did not include or exclude patients based on their cancer status.

Randomization Assignment Procedures

Randomization was accomplished with the Pocock Simon dynamic allocation procedure that balances the marginal distribution of the stratification factors between the treatment arms [22]. Stratification factors were comprised of the following: 1) gender: male versus female; 2) paclitaxel anticipated dose on day 1: </= 100 mg/m^2 versus > 100 mg/m^2; and 3) history of diabetes: yes versus no.

Treatment Intervention

In a double-blinded fashion, patients received auranofin 6 mg orally (2 capsules of 3 mg each) taken as a one-time dose on day #2 of the chemotherapy cycle (the day after paclitaxel administration) versus placebo 2 capsules taken orally on day #2 of the chemotherapy cycle. One-time administration was justified because this was a proof-of-concept study and because auranofin attains a peak plasma concentration at 1–2 hours with a half-life of 15 days [21,23].

Patient Assessments

Patient-reported outcomes were relied upon because these are considered the most meaningful indicators of symptoms [24,25]. Initially, patients were to complete the validated Brief Pain Inventory (modified) questionnaire daily on days 2 through 8 of the chemotherapy cycle as well as a concomitant pain medication diary [26–28]. Indeed, the primary endpoint focused on the modified Brief Pain Inventory item, “Please rate your pain by circling the one number that best describes your pain at its worse in the last 24 hours,” during days 2–8 of the study and as analyzed by means of area under the curve. Patients were also asked to complete a daily symptom summary questionnaire for days 2–8; the latter enabled patients to provide daily write in comments about their pain symptoms. Patients completed a questionnaire previously devised specifically to capture the PIAP syndrome at baseline [6].

Patients underwent a formal clinical assessment on either day 21 or day 28, depending on the date of their next chemotherapy assessment. At that visit, the above three questionnaires (the modified Brief Pain Inventory, the symptom summary questionnaire, and PIAP

syndrome questionnaire) were again completed. Adverse events were assessed by means of the Common Terminology Criteria Adverse Events (CTCAE), version 4.

Statistical Analyses

The primary endpoint was the percentage of patients who reported the PIAP syndrome in response to the item, “Please rate your pain by circling the one number that best describes your pain at its worse in the last 7 days,” as determined by area under the curve assessment. This item was followed by a 0 to 10 scale. Patient-reported quality of life scores were reported as per a transformed scale (0 to 100) with the highest score indicative of the most favorable symptomatology unless otherwise specified. We analyzed area under the curve for the worst daily pain scores over time and made direct comparisons between groups. Daily worst average pain scores were also directly compared between study arms. No adjustments were made for escalation of concomitant pain medications because no medications have previously been demonstrated to be effective in treating this pain. Comparisons were made with a two-sample t-test, Wilcoxon rank-sum test, Fisher’s test, or Chi square test, as appropriate. A p-value of < 0.05 was considered statistically significant. Other data, including concomitant pain medications and adverse events, are reported descriptively. Patient comments relevant to efficacy of auranofin or placebo are reported as direct quotes. The sample size was determined based primarily on pragmatic reasons. However, 30 patients (15 per arm) provided 80% power to detect an effect size of 1.06 standard deviation of the area under the curve.

RESULTS

Patient Characteristics

Thirty patients were enrolled from February 2014 through November 2015 with an equal distribution of assignment to auranofin versus placebo. Three patients (one auranofin patient and 2 placebo patients) did not complete the questionnaires for days 2–8 and were therefore excluded from the primary endpoint analyses (Figure 1).

Patients assigned to each study arm were similar in their baseline demographics (Table 1.) However, 6 patients in the placebo arm described baseline foot pain in contrast to one in the auranofin arm. Similarly, 5 patients in the placebo arm described baseline hip pain in contrast to one in the auranofin arm.

Pain Scores

The primary endpoint focused on the modified Brief Pain Inventory item, “Please rate your pain by circling the one number that best describes your pain at its worse in the last 24 hours,” which was to be completed on a daily basis during days 2–8 of the study and analyzed by means of area under the curve. Patient responses over time to the pain item, “Please rate your pain by circling the one number that best describes your pain at its worse in the last 24 hours,” yielded a mean area under the curve score of 55 units (standard deviation 19) and 61 units (standard deviation 22) in auranofin-treated and placebo-exposed patients, respectively (p=0.44). Similarly, comparing the means of worst pain scores on a daily basis over the preceding 24 hours yielded neither statistically not clinically significant

differences between groups (Figure 2). On day 4, considered the most severe time point for the PIAP syndrome, 78% of all patients described a score of 4 or worse pain (on a scale of 0 to 10 with the latter being worst), thus emphasizing the severity of pain in this syndrome.

Area under the curve for all other pain-related and quality of life questions on the modified Brief Pain Inventory showed no statistically significant differences between arms. On days 2 through 7, the worst average pain score on the modified Brief Pain Inventory remained consistently worse among auranofin-treated patients, although statistically significant differences were observed only on day 4 (with again worse pain with auranofin). However, on day 8 and at the end of the chemotherapy cycle (days 21 or 28), pain scores in the auranofin arm were more favorable compared to those in the placebo arm, although again these differences were not statistically significant. No other statistically significant differences in any of the other quality of life questions from the modified Brief Pain Inventory were observed between treatment arms.

The symptom summary instrument queried patients on type of pain -- asking whether it was sharp, dull, throbbing, cramping, stabbing, gnawing, burning, aching, heavy, splitting, shooting, stringing, or pulsating – and no statistically significant differences were observed between groups with two exceptions: on day 5, four placebo-exposed patients described “cramping” pain in contrast to none in the auranofin arm (p=0.02), and, on day 8, five placebo-exposed patients described “gnawing” pain in contrast to none in the auranofin arm (p=0.01). Additionally, location of pain by anatomic site was not statistically different between study arms with the exception that, on days 5 and 6, a statistically greater percentage of patients who received auranofin described upper extremity pain compared to those on placebo.

Interestingly, in response to the question at the end of the chemotherapy cycle (day 21 or 28), “In the last 7 days, how much relief have pain treatments or medications provided?” (followed by a response scale), all auranofin-treated patients described some pain relief in contrast to 2 placebo exposed patients; and 4 auranofin-treated patients described 100%, complete relief in contrast to 1 patient who received placebo (p=0.04) (Table 2).

Concomitant Pain Medications and Relevant Patient Comments

In the auranofin-treated group, 13 patients escalated their pain medications, and, in 2, changes could not be determined. Surprisingly, among placebo-exposed patients, 10 escalated their pain medications, and 3 did not. In two placebo-exposed patients, changed could not be determined.

Interestingly, in commenting on the efficacy of the study treatment, placebo-exposed patients noted, “The pain was not as bad as the first time I had chemo.” Another said, “After taking the pill or placebo, I feel the legs felt the best they had.” Yet another commented, “Normally, this would be the day when I would start to have some of my worst pain from the paclitaxel treatment…. However, I have had no pain or discomfort….” In contrast, another placebo-exposed patient reported, “The pills of the experiment had no effect for any relief! I must have gotten sugar pills in my opinion.”

Similarly, one auranofin-treated patient noted, “I think I must have gotten the placebo because I’ve had more pain today than any day since my chemo.” Another described, “Except for (migraine) headache, this cycle was much better.” Yet another reported, “The 2 pills I was given really helped me. I usually spend 5–6 days in bed, but never did after the pills.”

Adverse Events

No severe adverse events appeared directly attributable to the study intervention, and no statistically significant differences in rates of adverse events occurred between study arms (data not shown).

DISCUSSION

This study tested auranofin for the palliation of paclitaxel-induced pain within the context of a proof-of-concept, double-blinded, randomized, placebo-controlled trial and found that auranofin does not appear to palliate the PIAP syndrome. Patient-reported pain scores show that auranofin did not improve pain short-term in paclitaxel-treated patients. Interestingly, however, when asked about pain relief at the end of the chemotherapy cycle (day 21 or 28), auranofin-treated patients described greater pain relief at that time point, leaving open the possibility that auranofin may have provided a late palliative effect. Adding to the possibility of a late palliative effect, the modified Brief Pain Inventory showed that auranofin-treated patients reported less pain on day 8 as well as on days 21 or 28 of the chemotherapy cycle, although results did not reach statistical significance. When one considers the long 15-day half-life of auranofin, these late palliative effects appear plausible and suggest that perhaps the earlier administration of auranofin -- perhaps prior to the administration of chemotherapy – might have yielded greater palliative benefits.

In our opinion, despite the fact that this study’s primary endpoint was negative neutral, these secondary findings invite further study of auranofin as a potential palliative agent for the PIAP syndrome perhaps with the goal of starting the agent early and expecting pain control after the first week of therapy. Indeed, in patients with rheumatoid arthritis, a far more complicated disease process than the PIAP syndrome, the benefits of auranofin tend to be delayed after approximately three weeks of therapy [21]. Along similar lines, the fact that we tested only a single auranofin dose, which might not have readily penetrated into muscle, raises the possibility that repeated dosing might have yielded greater palliative effects.

This study provides two other interesting clinical findings. First, it underscores the severe nature of paclitaxel-induced pain. On day 4, which considered the peak of the PIAP syndrome, 78% of all patients described a score of 4 or worse pain on a scale of 0–10 with 10 being worse pain. Such severe pain scores occurred in the majority of patients and underscores that the PIAP syndrome continues to cause unmitigated distress for patients and therefore merits further clinical study. At the very least, the data presented here may help other investigators determine effect sizes needed as the PIAP syndrome is further studied. Secondly, in this study, we provided hand-written comments from patients about the study arm. Interestingly, some patients assigned to the placebo arm were convinced that they were

receiving active agent and vice versa and provide a rationale for incorporating a placebo arm in future trials aimed at mitigating the PIAP syndrome.

In summary, although this clinical trial did not achieve its primary endpoint, the comparative data between treatment arms are suggestive of a possible delayed benefit from auranofin. The efficacy of auranofin in treating this condition remains unknown, but these observations of delayed benefit merit further study, particularly in view of the fact that no effective therapy for paclitaxel-induced pain has yet to be discovered. In essence, these data clearly demonstrate that more effort should be put forth to understand the cause of this paclitaxel-induced pain, to palliate it, and potentially also to further study auranofin as long term palliative agent for the PIAP syndrome.

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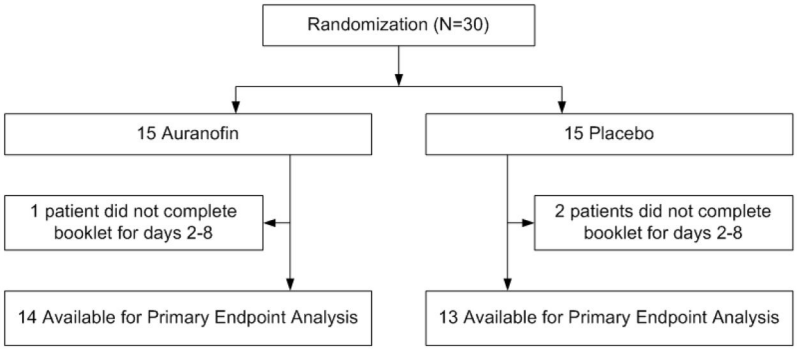

Figure 1.
The consort diagram shows study completion and questionnaire/booklet completion.

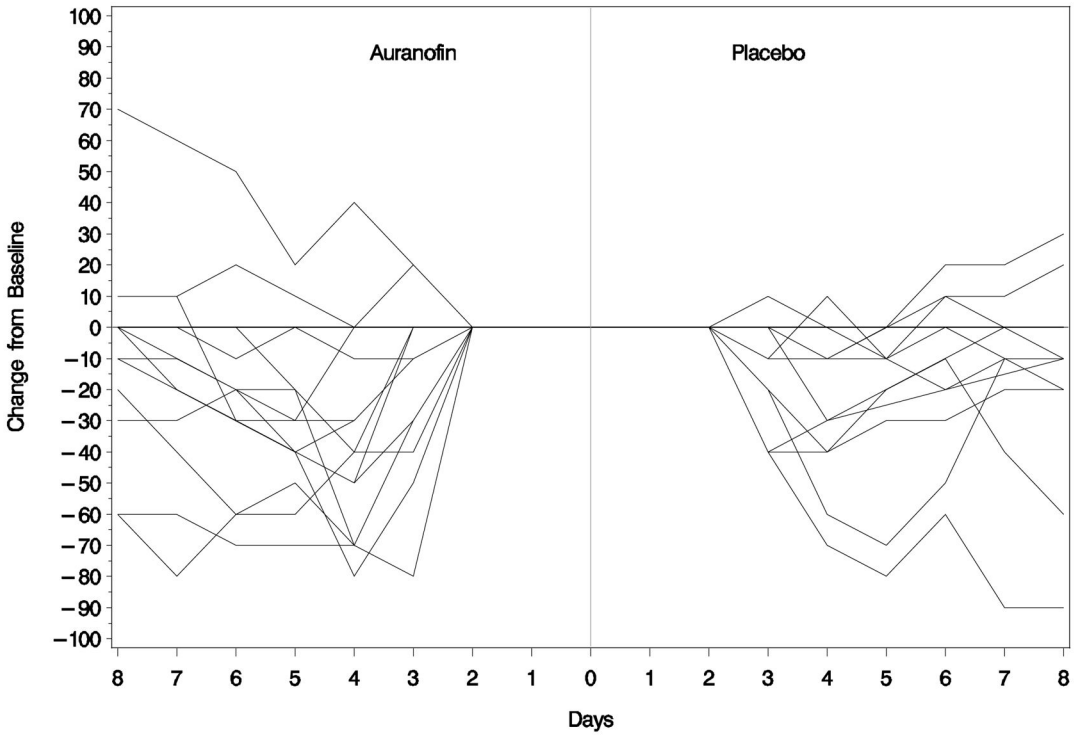

Figure 2.

Plot of Change from Baseline of Worst Pain

These plots shows change in 24-hour pain scores from baseline. By day 8, subtle suggestions of pain improvement were observed, although findings did not reach statistical significance.

Table 1

Demographics*

	Auranofin (n=15)	Placebo (n=15)	p-value
Mean age in years at enrollment (standard deviation)	63 (9)	57 (10)	0.18
Gender			
Female	12 (80)	13 (87)	0.62
Male	3 (20)	2 (13)	
Cancer			
Uterus	8 (53)	5 (33)	0.30
Lung	3 (20)	1 (7)	
Ovary	1 (7)	2 (13)	
Other	3 (20)	7 (47)	
Paclitaxel dose on day 1			
</= 100 mg/m^2	2 (13)	5 (33)	0.20
>100 mg/m^2	13 (87)	10 (67)	
Diabetes			
No	13 (87)	13 (87)	1.00
Yes	2 (13)	2 (13)	

*Numbers in parentheses denote percentages unless otherwise denoted.

Table 2

Number of Patients who Responded to the Day 21/28 Question, “In the last 7 days, how much relief have pain treatments or medications provided?”

Degree of Patient-Reported Pain Relief** (%)	Auranofin* (N=15)	Placebo*** (N=15)
0	0	2 (17)
10	0	1 (8)
20	0	0
30	0	0
40	1 (8)	0
50	0	0
60	1 (8)	0
70	0	2 (17)
80	4 (33)	0
90	2 (17)	6 (50)
100	4 (33)	1 (8)

*Numbers in parentheses denote the percentage of the cohort.

**Numbers may not sum to 100% because of rounding and missing data. Of note data are missing in 3 patients in each treatment arm.

***p=0.04 in comparisons across all responses in both groups.