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Case Study

The Role of Paracetamol (acetaminophen) in the Reduction of Tremor in Parkinson's Disease – a Case Study

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ABSTRACT

Parkinson's disease (PD) affects millions of people. Tremor is a common symptom. Treatment with levodopa can reduce tremor but is associated with "off periods" when the tremor returns as the dose wears off. The association of levodopa with neurotoxicity needs to be managed. This case study demonstrates the potential role of paracetamol (acetaminophen) in reducing tremor by extending the duration of levodopa efficacy. The case study aimed to confirm visual observations of tremor reduction associated with paracetamol medication. It utilised a mobile phone accelerometer and a software application to monitor the tremor of a subject with PD. The data produced provided information on frequency and variations in the intensity of the tremor. It was found that paracetamol alone does not appear to be effective at reducing tremor. The results show that paracetamol can reduce tremor in subjects during the period when their levodopa dose is usually wearing off particularly in the case of tremor concurrent with arm pain. There have been previous reports of a role for paracetamol or more particularly one of its metabolites, N-acetyl-p-benzoquinonimine, (NAPQI) in inhibiting pain signals in the spinal column. This could partly explain the theoretical basis for the reduction in tremor in this case.

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INTRODUCTION

Parkinson's disease (PD) is a progressive, debilitating neurological disease that afflicts approximately 2% of the population aged 65 or over (Cody et al., 2008). It is generally accepted that PD is related to a reduction in dopamine production in the brain (Beers and Berkow, 1999). The symptoms can be treated pharmacologically by the use of levodopa which can cross the blood brain barrier whereas dopamine cannot (Beers and Berkow, 1999). In the longer term, the dosage of levodopa has to be increased as dopamine supplementation becomes less effective at controlling symptoms, including tremor.

The symptoms of PD vary considerably between each individual. One characteristic early symptom is a tremor of limbs initially on one side of the body. This tremor is more visible while the arm is resting, hence the description "resting tremor". While the arm is active the tremor is suppressed. Tremor is a highly visible diagnostic feature. Temporary relief is

obtained with levodopa, however the tremor returns as the levodopa wears off, commonly known as the "off periods" (Beers and Berkow, 1999). Finding other means, such as repurposed drugs, to reduce tremor would be beneficial in improving the quality of life of patients and perhaps enable a reduction in levodopa, potentially reducing side effects.

The role of paracetamol in PD has been studied previously. Chen et al. (2005) found that paracetamol (acetaminophen) does not delay or prevent the onset of PD. However, studies by Cody et al. (2008) and Locke et al. (2008) imply an activity for paracetamol in the attenuation of dopamine neuron loss that leads to PD.

The subject of this case was diagnosed with PD seven years ago at the age 58. His left sided tremor responds to levodopa. It was noticed that during colds or flu or pain due to an injury to the arm or leg, the tremor worsened and taking paracetamol significantly reduced the tremor. The reduction in tremor at night was apparent during awakening periods, if

paracetamol was taken before bedtime and led to improved sleep.

The patient was in good compliance to the dosage regimen of levodopa, largely due to the recurrence of tremor acting as an indicator of the need for the next dose. The only time a levodopa dose was missed was once following a 1000 mg dose of paracetamol. The error was not realised until the following morning. This was 18 hours after the 12-noon levodopa dose the previous day. This case study describes a report in a single patient and provides preliminary evidence of this effect.

MATERIALS AND METHODS

The accelerometer in a mobile phone was used to monitor tremor. This utilised an application, available at the iStore, for approximately six dollars. This application, "Accelerometer Data Pro" created by Wavefront Labs, enabled the X, Y and Z accelerometer coordinates to be stored as a file which was exported into an Excel spreadsheet for processing. One benefit of this application was that sampling frequency (Hz) and sampling time could be varied.

The methodology used is in compliance to the previous reports such as in Daneault et al. (2013), who also used a smart phone to measure tremor. The data obtained was graphed and converted to the time domain using Fourier transforms to gain knowledge of the frequency range of the tremor. Rovini et al. (2017) carried out a thorough literature review of wearable sensors to support diagnosis of PD through monitoring of, among other symptoms, tremor. Most papers reviewed, used accelerometers to calculate features for tremor assessment. They concluded that smart phones, which do not require specific technical capability, could provide an alternative for a ubiquitous assessment in the clinical setting and in the home environment.

For each test in this study, the iPhone was held in the hand at approximately the same position with the arm at rest. In order to obtain valid data, a sampling frequency of approximately 25 - 50 Hz was used. About 2500 data points were collected periodically, over several hours, to monitor changes in tremor. Accelerometer data obtained in the X, Y and Z directions were both positive and negative in value. The square root of the sum of the squares of the coordinates was determined to provide a single positive number for the tremor reading. Each figure was broken up into a series of readings covering approximately 100 seconds sampling period. The graphs record periodic batches of data and not a continuous record of the tremor.

The data was also subjected to fast Fourier analysis using Excel, to examine the changes in frequency and intensity of the tremor following the ingestion of paracetamol.

The levodopa medication used, as prescribed by a neurologist, was Stalevo 200mg (Novartis Pharmaceutical Australia Pty Limited) containing Levodopa 200mg, Carbidopa 50mg, and Entacapone 200mg. The levodopa was routinely administered three times a day at 6 hourly intervals from 6am with no dose during night. The paracetamol (acetaminophen) employed was Panamax (Sanofi Aventis) containing paracetamol 500mg. A dose of 2x500mg paracetamol was employed during each test. Other PD medication routinely taken was pramipexole (Sifrol), Boehringer Ingelheim 1.5mg extended release, 1 per day. The pramipexole dose was not varied during the various tests.

Tests were also carried out without paracetamol to show the normal variability of the tremor with "on time" and "off time" of the levodopa. Further test employed a single dose of paracetamol 2x500mg to demonstrate the reduction in tremor and the correlation of tremor reduction with the pharmacological activity of paracetamol. Another test involved taking two doses of paracetamol approximately 3.5 hours apart to examine the potential of a multi-dose protocol to reduce tremor over a longer period and to thus extend the levodopa "on time". Levodopa was not taken in one test to test the use of paracetamol alone.

Formal Ethics Committee approval was not available as this was a private investigation and the author was the subject of the test which involved self-medication with a common analgesic. All medications used were within manufacturers or neurologists dose recommendations.

RESULTS AND DISCUSSION

Figure 1 shows five sets of readings (A, B, C, D, and E) taken over a 6-hour period commencing prior to the morning dose of levodopa. It demonstrates the effect of levodopa in reducing tremor (B and C) and the wearing off of the levodopa (D and E) as the tremor returns. Figure 1 shows the complete cycle from one "off period" to the next "off period". The other figures cover an extended period to demonstrate the extended "on period" when using paracetamol with levodopa.

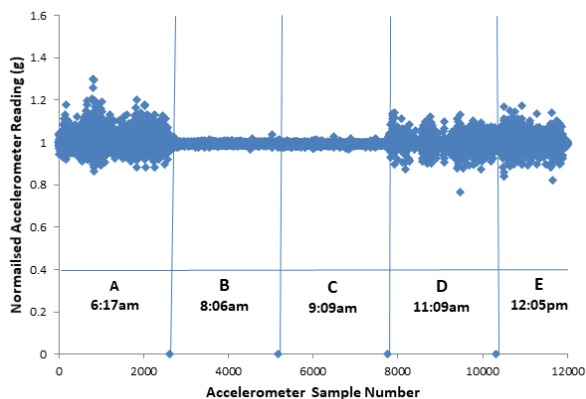


Fig. 1 Shows tremor readings without paracetamol. Tremor readings "A" were taken upon awakening, 12 hours after last dose of levodopa. Levodopa was taken following reading "A". Further readings were at B = 109 minutes, C = 172 minutes, D = 292 minutes and E = 348 minutes after morning dose of levodopa.

Figure 2 shows a reduction in tremor with a single paracetamol treatment taken at 11:36 am immediately after readings "D" as the levodopa wore off and tremor returned. There is a significant reduction in tremor at times "E", "F" and "G". In this case there was some arm pain present at the time of readings. The pain level was assessed using the Visual Analogue Pain Scale (VAS). On a scale of 0 to 100 the pain level in the arm was assessed as being 25. Although arm and shoulder pain is common in PD, in this case it is unclear if the pain is due to PD or to other factors. The extension of levodopa efficacy was greater when pain was present. This points to a possible association of pain and tremor.

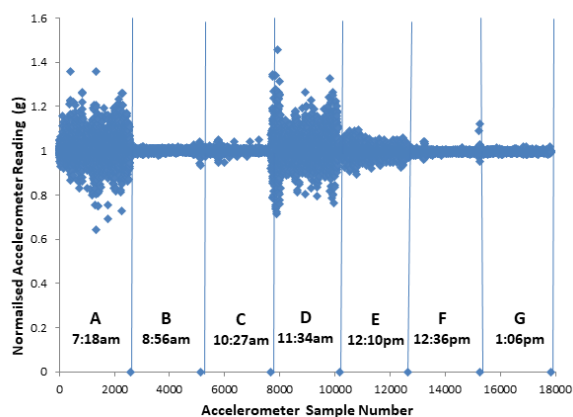


Fig. 2. Shows a reduction in tremor with a single paracetamol treatment taken at 11:36 am after readings "D" (arm pain present). Readings "A" shows tremor upon awakening - 13 hours after last levodopa medication, B = 98, C = 129, D = 196, E = 233, F = 259, G = 289 minutes after the 7:20am levodopa dose.

Figure 3 repeated the test in Figure 2 and showed a similar but lesser reduction in tremor. Comparing

Figure 2 and 3 it is noted that the reduction in tremor in Figure 3 although still present, is not as dramatic as in Figure 2. Measurements shown in Figure 2 were taken when there was significant arm pain, whereas Figure 3 measurements were taken at a time when there was little or no arm pain. The paracetamol medication was more effective in reducing tremor at a time when arm pain was present.

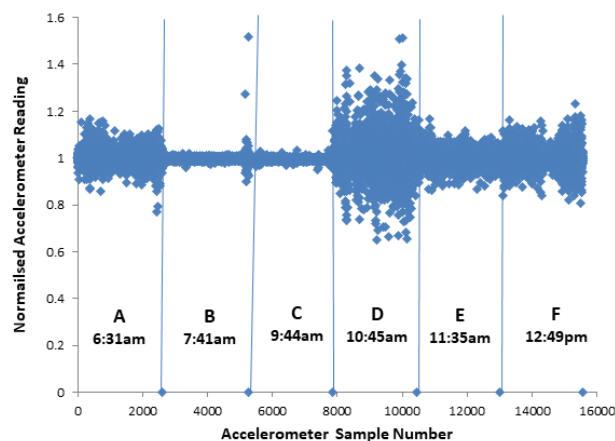


Fig. 3. Readings "A" shows tremor upon awakening - 12 hours after last levodopa medication. Levodopa was taken after readings "A". It demonstrates a reduction in tremor with a paracetamol dose taken after readings "D". Arm pain was not present.

Figure 4 demonstrates the effect of two, time separated doses of paracetamol on tremor. The first dose was taken after reading "A" with the initial dose of levodopa. A second paracetamol dose was taken prior to the beginning of the "off period" after reading "C". It demonstrates the suppression of tremor which effectively extended the efficacy of the levodopa.

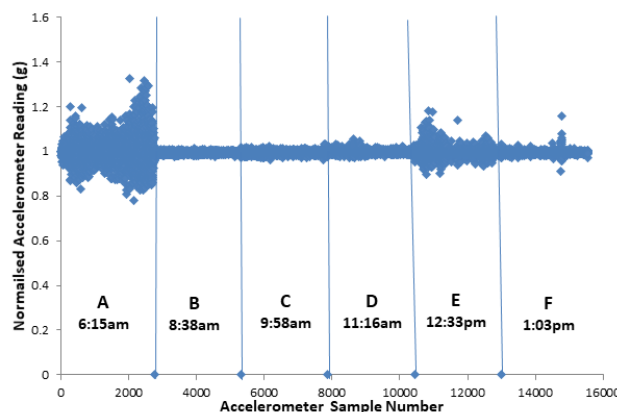


Fig. 4. Shows tremor readings with two paracetamol treatments: Readings "A" shows tremor upon awakening - 13 hours after last levodopa dose. Levodopa was then taken after reading "A". Paracetamol was also taken at 6:15am after readings "A" and a second dose after the 9:58am readings "C".

Figure 5 tested the effect of paracetamol alone on tremor. There was no significant reduction in tremor. The tremor continued to increase over the morning. This indicates that paracetamol alone is not effective in reducing tremor but from other observations, that it acts synergistically with the levodopa to minimize tremor. Pramipexole (Sifrol) was taken in all tests. This figure shows that pramipexole (Sifrol) and paracetamol did not act synergistically to reduce tremor. Figure 6 show fast Fourier analysis of the tremor data. It shows the presence of a 4-6hz tremor peak 330 minutes after the previous levodopa dose. This frequency is typical of Parkinson's tremor (Chen et al., 2005). Figure 6 has a less intense peak 4-6 Hz peak 47 minutes after the paracetamol. The peak is further reduced 125 minutes after the paracetamol.

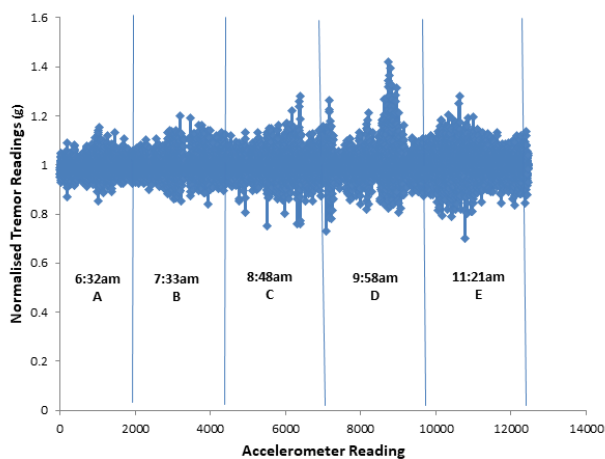


Fig. 5. Shows tremor readings commencing 12 hours after the previous dose of levodopa and with a paracetamol dose taken immediately after readings "A". No further levodopa was taken.

These results have been replicated over a 12-month period and align with visual observations of tremor reduction following paracetamol ingestion. Statistical analysis of data sets (F-Test) confirmed the visual assessment of the reduction in tremor in the presence of paracetamol or its metabolite. In Figure 2 there was a significant difference between tremor before paracetamol D, ($X=1.012$, $SD = 0.070$) to after paracetamol E ($X = 0.9968$, $SD = 0.0192$), $F_{(2495, 2457)} = 13.41$, $p < 0.05$). In Figure 2 there was a significant difference between tremor before paracetamol E ($X=0.996$, $SD = 0.01918$) to after paracetamol F ($X = 0.995$, $SD = 0.006$), $F_{(2457,2631)} = 9.625$, $p < 0.05$). In Figure 4 there was a significant difference between tremor before second paracetamol E, ($X=0.994$, $SD = 0.021$) to after the second paracetamol F ($X = 0.9945$, $SD = 0.0069$), $F_{(2561,2548)} = 9.00$, $p < 0.05$). In Figure 4 there was no significant difference between tremor before second paracetamol D, ($X=0.998$, $SD = 0.0071$) to after the second paracetamol at F ($X = 0.994$, $SD = 0.00698$), $F_{(2572,2549)} = 1.056$, $p < 0.05$). These two sets of readings

were separated by a significantly different tremor E (above).

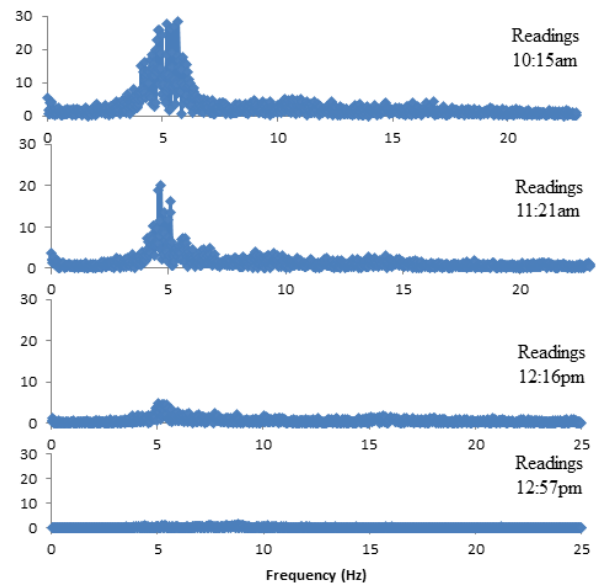


Fig. 6. Fast Fourier analysis of tremor data at various times after levodopa 6:15am and paracetamol dose at 10:20am showing a reduced 4-6 Hz tremor peak over time.

Metabolism and pharmacokinetics of paracetamol have been extensively studied (Ameer and Greenblatd, 1977; Cummings et al., 1967; Forrest et al., 1982). It is known to be rapidly absorbed from the gastrointestinal tract, giving peak plasma concentrations about one hour after ingestion, and being cleared from plasma with a half-life of approximately two hours if the individual has normal hepatic function (Steventon et al., 1990). The pharmacokinetics of paracetamol relate well to the improvement in tremor over a 1.5 hour period shown in Figure 2 as the serum concentration of paracetamol and breakdown products increase. In Figure 5 no levodopa was taken. In this case the paracetamol alone did not reduce tremor. The data indicates that paracetamol alone does not significantly reduce tremor but when used in combination with levodopa extends the effectiveness of the levodopa.

Apomorphine acts as a dopamine agonist and is clinically used to treat PD. Schulze et al. (2013) showed that apomorphine acts on endogenous transient receptor potential ankyrin type-1 (TRPA1) in cultured dorsal root ganglion neurons from rats. This indicates a link between Apomorphine, an accepted Parkinson's medication, and TRPA1. The mechanism of the effect of paracetamol and its breakdown product on nerve transmission also relates to TRPA1 (Andersson et al., 2011).

It has been established recently that when paracetamol is given, one of its break-down products, N-acetyl-p-benzoquinonimine (NAPQI), activates a protein on the surface of nerves in the spinal cord and reduces the nerve cell's ability to transmit pain signals (Andersson et al., 2011). A co-author of this discovery, Bevan, discussed these findings; *'What we saw happening in the mice was that the break-down product formed from paracetamol in turn stimulates a protein found on the surface of nerve cells called TRPA1. When this protein was activated, it appeared to interfere with the transmission of information from that nerve cell to other nerve cells, which would normally send a signal up to the brain, signalling pain. So in this case the NAPQI product that was formed from paracetamol acted on the TRPA1 protein to reduce transmission of information from pain-sensing nerves to the brain'* (King's College London, 2011).

Steventon et al. (1990) also discussed the metabolism of paracetamol in patients with PD. They found patients with PD had a decreased capacity to form the sulphate conjugate metabolite. They noted that chronic dosage with even therapeutic doses of paracetamol may further deplete sulphate levels thus decreasing the capacity to form excretable metabolites. This may make certain individuals susceptible to toxicity, even at doses currently accepted as safe. It may also reduce the capacity to excrete other toxins which utilise the same pathway.

Arm and shoulder pain and muscle strain does appear to aggravate tremor. It has been shown that paracetamol with levodopa can reduce tremor when pain is present (Figure 1 and 2). The effect was not so obvious when arm pain was not present (Figure 3). The author also noted an increase in tremor at times when muscles were sore as result of exercise, attempting to keep the arm still, or even carrying a heavy weight. Paracetamol medication for Parkinson's tremor, could reduce perception of pain signals by reducing the signal sent by an injury or strained muscle, to the brain. It could be postulated that the perception of pain by the brain could lead to a tremor signal. Further research is required to determine if paracetamol also suppresses nerve signals coming from the brain initiating the tremor.

Being a resting tremor, it can be reduced by distraction. This needed to be avoided or minimized while taking the batches of accelerometer readings. However, the author's observations are that, distraction does not produce the same long-term effect, reducing tremor for 3-5 seconds, much shorter than the figures demonstrate with paracetamol.

PD is incurable, so involves lifelong medication protocols. Levodopa is notorious for becoming less

effective over time (Beers and Berkow, 1999). The safety and efficacy of long-term therapy with paracetamol to reduce tremor needs to be considered. Long term use of paracetamol is common in osteoarthritis cases (Beers and Berkow, 1999). Repurposing the drug for PD disease, to extend the effectiveness of levodopa, in receptive individuals, should not require excessive safety investigation provided the maximum daily dose is not exceeded. This dose needs to be assessed taking into account the decreased ability of Parkinson's patients to metabolise paracetamol (Steventon et al., 1990).

CONCLUSIONS

In this case study, observation and quantitative tremor measurement, suggest that paracetamol has the potential to reduce the severity of PD related tremor by extending the "on time" and thus the efficacy of the levodopa. Importantly, paracetamol is not effective by itself in the absence of levodopa.

PD symptoms vary between individuals. Tremor is not present in all cases (Chen et al., 2005). These variables and the possibility of a placebo effect would require further investigation through randomised double-blinded cross over trials. Further studies would be desirable utilising continuous tremor monitoring. These results present a promising avenue for PD treatment and research.

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