

RÉSUMÉ

DONNÉES DE BASE: On a observé une incidence élevée de réaction anaphylactoïde durant un essai de phase I/II utilisant des doses élevées de cyclosporine par voie intraveineuse. Des recherches épidémiologiques ont alors révélé que la survenue de ces réactions anaphylactoïdes était associée de façon significative à un mélange inapproprié de la perfusion au moment de la préparation. On a émis l'hypothèse que le mélange inadéquat au moment de la préparation de la perfusion a pu résulter en une injection initiale constituée principalement du véhicule de la perfusion, soit le Crémophor EL. Ces injections initiales pourraient avoir causé les réactions anaphylactoïdes.

OBJECTIF: Étudier l'effet de différentes techniques de brassage sur la distribution des composantes du concentré de cyclosporine pour perfusion (Sandimmune IV) dans les solutions administrées aux patients. Les composantes sont la cyclosporine, le Crémophor EL et l'éthanol.

MÉTHODES: Les perfusions ont été préparées de façon similaire à celles administrées aux patients participant à l'étude de la cyclosporine utilisée à doses élevées. Des échantillons ont été recueillis à des moments précis

de la perfusion. Les concentrations de cyclosporine et de Crémophor EL ont été déterminées par spectrophotométrie et les concentrations d'éthanol ont été mesurées de façon enzymatique.

RÉSULTATS: Les concentrations de cyclosporine et de Crémophor EL étaient jusqu'à neuf fois plus élevées que prévues durant les 10 premières minutes lorsque les perfusions n'étaient pas mélangées de façon appropriée. Par opposition, les concentrations de cyclosporine et de Crémophor EL étaient telles que prévues quand les perfusions étaient bien mélangées.

CONCLUSIONS: Le mélange inadéquat des perfusions de cyclosporine à dose élevée peut conduire à l'administration d'une injection initiale plus concentrée de cyclosporine et de Crémophor EL. Les concentrations élevées de Crémophor EL ont été associées à des réactions anaphylactoïdes. Dès lors, le mélange adéquat des perfusions de cyclosporine à dose élevée peut être important pour diminuer la survenue de réactions anaphylactoïdes dangereuses pour la vie des patients.

MARIE LAROCHE

Ambulatory Care

FORMULATION AND STABILITY OF NALTREXONE ORAL LIQUID FOR RAPID WITHDRAWAL FROM METHADONE

J Paul Fawcett, Nicola C Morgan, and David J Woods

OBJECTIVE: To assess the stability of naltrexone oral liquid prepared from tablets and powder, and to evaluate its use in precipitating rapid withdrawal from methadone.

DESIGN: Naltrexone 1 mg/mL oral liquids were prepared from tablets and powder and stored in the dark at 4, 25, and 70 °C. Similar formulations containing 5 mg/mL were stored at 70 °C. The 1-mg/mL formulation prepared from tablets was clinically evaluated in inducing rapid withdrawal in two drug-dependent individuals receiving methadone maintenance treatment using a naltrexone dose titration protocol.

SETTING: A university pharmacy school and affiliated urban teaching hospital.

MAIN OUTCOME MEASURES: Samples removed at six time points were analyzed for naltrexone concentration to assess decomposition over

90 days. An opioid withdrawal symptom checklist was used to assess the severity of the withdrawal symptoms prior to, and 30 minutes after, each dose of naltrexone.

RESULTS: Decomposition of naltrexone in all formulations stored at 4 and 25 °C was not significant over 90 days. Both patients tolerated naltrexone 1 mg/mL oral liquid, but found it bitter and gritty. Withdrawal symptoms were experienced immediately after the first dose, but were resolving by the end of day 3 of naltrexone treatment, at which stage both patients were able to tolerate a 50-mg tablet of naltrexone as maintenance.

CONCLUSIONS: Naltrexone 1 mg/mL oral liquids prepared from tablets or powder are stable when stored in the dark for 60 days at 4 °C and for 30 days at 25 °C. The formulation prepared from tablets provides flexible dosing in patients undergoing rapid withdrawal from methadone.

KEY WORDS: naltrexone, methadone.

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METHADONE MAINTENANCE TREATMENT (MMT) was introduced over 30 years ago¹ and is now the most widely used treatment for narcotic addiction.^{2,3} Patients who want to overcome their addiction face a protracted withdrawal with

unpleasant symptoms that persist for 2 or 3 weeks. This sustained period of withdrawal leads many drug-dependent individuals to relapse and either rejoin MMT or even revert to intravenous drug use. Rapid withdrawal with an orally active narcotic antagonist combined with aggressive treatment of symptoms can be useful for addicts who have sufficient motivation to live an opiate-free lifestyle.^{4,5}

Naltrexone is an orally active narcotic antagonist used to precipitate withdrawal and prevent relapse in detoxification from methadone.^{6,7} A planned detoxification protocol requires an initial dose as low as 1 mg followed by dosage titration according to the level of discomfort the patient can tolerate.^{8,9} Withdrawal is initiated on an inpatient basis and symptoms are attenuated by using clonidine, benzodiazepines, and possibly quinine and *N*-butylscopolamine bromide for muscle cramps and abdominal cramps, respectively. After 4 days, patients are generally able to initiate naltrexone maintenance based on a daily 50-mg tablet (Trexan, DuPont Merck Pharmaceutical Co., Wilmington, DE). Naltrexone maintenance allows time for rehabilitation to a lifestyle free from the environmental stimuli that promoted narcotic use.¹⁰

The flexibility of dosing with naltrexone required in a detoxification protocol is readily achieved by using an oral liquid. In 1976, the National Institute for Drug Abuse (NIDA) of the US suggested a suitable 10-mg/mL formulation (Appendix I), but no information is available regarding its stability or clinical use (personal communication, AP Cuccia, DuPont Pharmaceuticals, Wilmington, DE, December 1992). The aim of this study was to formulate extemporaneous naltrexone oral liquids from tablets and powder, evaluate their shelf-lives, and investigate the use of a formulation based on tablets in promoting rapid withdrawal from methadone.

Methods

FORMULATIONS

Formulations of naltrexone oral liquid (1 and 5 mg/mL) were prepared from tablets^a and powder^b and contained ascorbic acid^c (0.5%), sodium benzoate^d (0.1%), glycerol^e (20%), and distilled, deionized water (to 100%). The vehicle was based on a modification of the NIDA formulation and the naltrexone concentrations were selected to provide easy and flexible dosage titration. The 1-mg/mL formulation was prepared with and without filtration to investigate the effect of insoluble tablet excipients. The formulations were prepared by triturating crushed tablets or powder with the ascorbic acid and sodium benzoate, adding the glycerol to form a paste, and making up to volume with water. Aliquots (50 mL) were transferred into 50-mL amber, high-density polyethylene bottles with polypropylene screw-top lids.^f

SAMPLING AND STORAGE

Five bottles of the unfiltered tablet and powder 1-mg/mL formulations and one bottle of the filtered 1-mg/mL tablet formulation were stored in the dark at each of three temperatures: 4, 25, and 70 °C. An additional bottle of the powder and unfiltered tablet formulations were stored at each temperature and were used to assess changes in color, odor, and pH. Five bottles of each 5 mg/mL formulation were stored at 70 °C. Samples (1 mL) were removed after manual shaking on days 0, 10, 20, 30, 60, and 90, placed in 2-mL Cryolok vials^g and frozen at -70 °C until analysis. The pH was monitored with a polymer pH combination electrode.^h On the day of assay, samples were allowed to thaw at room temperature. After shaking, aliquots (100 µL) were diluted to 1.0 mL (1 mg/mL formulation) or 5.0 mL (5 mg/mL formulation) with mobile phase, centrifuged at 2000 revolutions per minute for 5 minutes to separate insoluble excipients, and injected into the HPLC system.

HPLC ASSAY

The HPLC assay for naltrexone was based on that of Asali et al.¹¹ The HPLC system consisted of a JASCO solvent delivery system,ⁱ a variable-wavelength ultraviolet detector^j set at 214 nm, and an automatic sampler^k set to inject 10 µL. A computerized chromatography data analysis system^l was used for data acquisition and analysis. The stainless-steel column (25.0 cm × 4.6 mm internal diameter) containing 5 µm resin^m was operated at ambient temperature. The mobile phase consisted of 50% acetonitrileⁿ and 50% of a solution of triethylamine^o 0.06% in monobasic potassium phosphate buffer^p (40 mM) pH 5.0 at a flow rate of 1.0 mL/min. Under these conditions, the retention times of ascorbic acid, sodium benzoate, and naltrexone were 2.2, 3.0, and 6.0 minutes, respectively.

ASSAY VALIDATION

Three independently prepared stock solutions of naltrexone powder in water (1 mg/mL) were prepared and diluted to concentrations of 0.2, 0.1, 0.05, 0.02, and 0.01 mg/mL. The calibration curve based on peak height was linear ($r^2 > 0.99$), with an intercept not significantly different from 0. The intraday coefficient of variation (CV), measured by analyzing a 0.1 mg/mL naltrexone solution five times consecutively on the same day, was 3.4%. The interday CV, measured by analyzing a sample of 0.1-mg/mL naltrexone solution five times on 3 separate days, was 9.7%.

To demonstrate that the assay was stability indicating, solutions (nominally 0.1 mg/mL) of a freshly prepared standard and of the powder formulation before and after storage at 70 °C for 90 days (70% decomposition) were analyzed by HPLC using detector wavelengths of 214 and 220 nm. The ratio of peak heights at 214 versus 220 nm was 0.61, 0.60, and 0.66 for the freshly prepared standard, the unstressed sample, and the stressed sample, respectively, indicating the naltrexone peak was free of interference from decomposition products.

DATA ANALYSIS

For each formulation, the mean peak heights of the five samples at each time point were determined and converted to percentages of the corresponding day 0 values. These data were analyzed by linear regression by using a validated computer program (Pharmaceutical Statistical

^aTrexan (naltrexone) tablets, lot no. FN220A, DuPont Merck Pharmaceutical Co., Wilmington, DE.

^bNaltrexone hydrochloride powder, lot no. 101H0168, AnalaR grade, Sigma Chemical Co., St. Louis, MO.

^cAscorbic acid BP, lot no. 17284, Pharmaceutical Sales and Marketing, Auckland, New Zealand.

^dSodium benzoate, AnalaR grade, lot no. 6460950, Ajax Chemicals Pty. Ltd., Auburn, New South Wales, Australia.

^eGlycerol, lot no. 22824C, Pharmaceutical Sales and Marketing, Auckland, New Zealand.

^fMultichem Laboratories Ltd., Auckland, New Zealand.

^gCryolok vials, Biotek, Auckland, New Zealand.

^hModel E8080, EDT Instruments, Kent, UK.

ⁱModel 880-PU, Japan Spectroscopic Co. Ltd., Tokyo, Japan.

^jModel 873-UV, Japan Spectroscopic Co. Ltd., Tokyo, Japan.

^kShimadzu SIL9A, Shimadzu Corp., Kyoto, Japan.

^lDelta V4.01 Digital Solutions Pty., Margate, Queensland, Australia.

^mSupelcosil LC-18 DB, Supelco, Bellefonte, PA.

ⁿAcetonitrile HPLC grade, Ajax Chemicals Pty. Ltd., Auburn, New South Wales, Australia.

^oTriethylamine, analytical grade, BDH Chemicals Ltd., Poole, England.

^pMonobasic potassium phosphate, AnalaR grade, May and Baker Ltd., Dagenham, England.

Regression, School of Pharmacy, University of Otago). Decomposition was significant ($p < 0.05$) if the slope of the regression line was less than zero (1-tailed Student's *t*-test). In these cases, rate constants with 95% CIs for the most appropriate kinetic model were calculated.

CLINICAL STUDY

To evaluate the naltrexone oral liquid in clinical practice, two drug-dependent individuals receiving MMT through the local Community Alcohol and Drug Service (1 man aged 27 y and 1 woman aged 32 y) volunteered to undergo opioid withdrawal using a protocol based on those of Charney et al.⁸ and Brewer et al.⁹ Since naltrexone is not registered in New Zealand, the protocol was approved by the Southern Regional Health Authority Ethics Committee (Otago) and volunteers gave their written, informed consent. Both patients had been receiving MMT for at least 2 years and were stabilized on 50 mg/d before reducing their daily dose prior to entering the study to 35 mg (the man) and 14 mg (the woman).

The patients were admitted to the hospital the day after their last dose of methadone and, after a physical examination, were administered a 1-mg dose and, after 4 hours, a 2-mg dose of naltrexone 1 mg/mL oral liquid. On the day after admission (day 2), they received naltrexone 4, 6, 8, and 10 mg at 4-hour intervals; on day 3, doses of 10, 12, 12, and 15 mg were given. If withdrawal symptoms were distressing, naltrexone was withheld until the symptoms were well controlled with clonidine (tablets or patches) and, if necessary, diazepam. Blood pressure was monitored and clonidine was withheld if the blood pressure dropped below 90/60 mm Hg. Quinine sulfate and *N*-butylscopolamine bromide were also available if required for muscle and abdominal cramps, respectively. On day 4, the patients were given a naltrexone 50-mg tablet and, 1 hour later, were discharged on naltrexone 50 mg/d maintenance therapy. A checklist comprising 33 symptoms associated with opioid withdrawal was administered when the patients were first admitted and prior to and 30 minutes after each dose of naltrexone. The severity of each symptom was graded on a four-point scale from nil through severe.

Results

FORMULATION STABILITY

Decomposition of naltrexone in unfiltered tablet and powder formulations stored at 4 and 25 °C was not significant over 90 days (Table 1). At 70 °C, decomposition was significant ($p < 0.05$) and was adequately described by a zero-order model. The rates of decomposition of formulations prepared from powder (3.9 ± 0.6 µg/mL/d) and un-

tered tablets (3.6 ± 0.3 µg/mL/d) at 70 °C were not significantly different and were unaffected by the naltrexone concentration. Removal of the insoluble tablet excipients by filtration did not appear to affect the rate of decomposition at 70 °C (data not shown).

In terms of physical stability, powder formulations in storage at 4 °C remained clear, but became pale yellow after 90 days. At 25 °C, these formulations became yellow by day 60; at 70 °C, a yellow color began to appear at day 2 and, by day 30, they were brown. In all cases the pH fell slightly from 3.5 to 3.2 over 90 days. A similar pattern was observed in the tablet formulations in which the yellow color was superimposed on a slight orange color imparted to the formulations by tablet excipients.

CLINICAL STUDY

Both patients tolerated the naltrexone 1-mg/mL oral liquid, but found it very bitter and gritty. They both experienced immediate symptoms of withdrawal after the first dose of naltrexone, particularly restlessness, muscle and stomach cramps, muscle spasms and stiffness, hot and cold flashes, loss of appetite, and malaise. The woman also felt very anxious and had great difficulty sleeping throughout the protocol. The man took regular doses of clonidine and found it very helpful, whereas the woman, wearing a clonidine patch, required diazepam 10 mg q4h. Both patients took an occasional dose of quinine and *N*-butylscopolamine bromide, but found these agents only partially controlled muscle and abdominal cramps. By the end of day 3, symptoms were resolving and both patients were able to tolerate a 50-mg tablet of naltrexone before being discharged on naltrexone maintenance. The two patients continued the medication for about 1 month and then felt able to discontinue naltrexone.

Discussion

To provide a simple formulation of naltrexone oral liquid, the NIDA formulation was modified by replacing the

Table 1. Stability of Naltrexone Oral Liquids Prepared from Tablets or Powder in Storage for 90 Days (n = 5)^a

TEMPERATURE (°C)	INITIAL CONCENTRATION (mg/mL)	PROPORTION OF DAY 0 CONCENTRATION (%)					
		DAY 0	DAY 10	DAY 20	DAY 30	DAY 60	DAY 90
Tablet (1 mg/mL)							
4	1.01 ± 0.05	100.0 ± 5.0	100.2 ± 1.1	99.3 ± 1.9	103.2 ± 2.3	103.9 ± 2.8	99.1 ± 3.7
25	0.99 ± 0.04	100.0 ± 4.0	102.1 ± 3.1	102.4 ± 5.8	101.9 ± 3.7	104.1 ± 4.0	101.7 ± 5.2
70	0.99 ± 0.04	100.0 ± 4.0	100.4 ± 3.8	92.9 ± 1.9	89.9 ± 1.2	79.8 ± 4.0	54.5 ± 4.0
Tablet (5 mg/mL)							
70	4.70 ± 0.15	100.0 ± 3.2	100.0 ± 5.0	92.5 ± 5.0	82.2 ± 5.0	84.0 ± 6.6	51.1 ± 3.0
Powder (1 mg/mL)							
4	0.97 ± 0.04	100.0 ± 4.1	101.1 ± 2.7	100.3 ± 2.1	101.8 ± 2.8	101.4 ± 2.0	101.3 ± 4.9
25	0.96 ± 0.04	100.0 ± 4.2	95.7 ± 5.1	97.8 ± 5.0	100.3 ± 3.1	97.8 ± 3.0	90.3 ± 3.0
70	0.96 ± 0.04	100.0 ± 4.2	97.6 ± 1.0	94.1 ± 2.0	89.4 ± 3.0	83.5 ± 3.3	61.2 ± 4.0
Powder (5 mg/mL)							
70	5.05 ± 0.05	100.0 ± 1.0	93.6 ± 3.0	93.6 ± 4.0	85.9 ± 3.5	88.5 ± 3.0	64.1 ± 4.9

^aAll values are mean ± SD.

sorbitol with glycerol and by omitting the flavoring and coloring agents. A formulation prepared from tablets was included in the study to allow for situations in which powder is unavailable. The ascorbic acid is included to provide a sufficiently low pH to ensure antimicrobial activity of the sodium benzoate. However, microbial growth in the formulations in storage was not assessed in this study.

Based on the absence of significant chemical degradation in the naltrexone oral liquids stored at 4 or 25 °C, it appears they can be prepared from either tablets or powder. Their shelf-life is limited by physical instability, as revealed by the development of color. On this basis, shelf-lives of 30 and 60 days can be assigned to formulations stored at 25 and 4 °C, respectively. Formulations prepared from crushed tablets may be filtered to remove insoluble excipients and thereby improve the appearance of the product. Filtration does not appear to affect the final concentration of naltrexone or the stability of the oral liquid.

Although clinical evaluation of the naltrexone oral liquid was limited to the unfiltered 1-mg/mL formulation prepared from tablets administered to only two patients, it appears to be well tolerated except for its bitter taste. Mixing the dose with fruit juice or a flavored drink prior to administration may overcome this problem. It is also possible to use a naltrexone 5-mg/mL formulation to reduce the volume required at the higher dosages. In the absence of stability data for this formulation, a shelf-life of 7 days at 4 °C is appropriate. Alternatively, naltrexone powder could be repackaged into gelatin capsules, but this would be time-consuming and would not provide dosage flexibility.

Withdrawal symptoms of narcotic addiction are unpleasant and, in the case of a drug with a relatively long half-life such as methadone, can last for up to 2 weeks following abrupt discontinuation. The use of naltrexone oral liquid in our patients, combined with aggressive palliative care, resulted in a rapid and relatively uneventful withdrawal with the resolution of most symptoms after only 3 days. The availability of a stable naltrexone oral liquid makes it practical to prepare a stock bottle and thereby reduce waste in a drug clinic where several patients may be simultaneously undergoing rapid withdrawal from MMT.

Summary

Naltrexone 1 mg/mL oral liquids prepared from tablets and powder are chemically stable for at least 30 days when stored in the dark at 4 and 25 °C. The formulations appear to be clinically acceptable and provide flexible and convenient dosage forms for use in promoting rapid withdrawal from methadone addiction. ≡

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EXTRACTO

OBJETIVO: Estimar la estabilidad de naltrexona oral en forma líquida preparada de tabletas, y polvos, y evaluar su uso en acelerar el deshabituamiento de la metadona.

DISEÑO: Se prepararon líquidos orales de naltrexona con tabletas y con polvos, y se almacenaron en oscuro a 4, 25, y 70 °C. Fórmulas similares que contenían 5 mg/mL se almacenaron a 70 °C solamente. Se evaluó clínicamente el efecto de la fórmula de 1 mg/mL que se preparó con tabletas al utilizarse para inducir el deshabituamiento rápido en dos adictos que estaban bajo tratamiento de mantenimiento con metadona usando un protocolo de dosificación de naltrexona.

ESCENARIO: Una escuela universitaria de farmacia y un hospital docente urbano afiliado.

MEDICIÓN DE RESULTADOS: Las muestras que se obtuvieron a 6 diferentes períodos de tiempo se analizaron para estimar la descomposición del líquido durante 90 días. Se utilizó una lista de síntomas de abstinencia de opioides para estimar la severidad de estos antes, y media hora después de cada dosis de naltrexona.

RESULTADOS: No hubo descomposición significativa durante 90 días de ninguna de las fórmulas almacenadas a 4 ° y 25 °C. Ambos pacientes toleraron el líquido de naltrexona de 1 mg/mL aunque lo sintieron amargo y arenoso. Experimentaron síntomas de abstinencia de inmediato luego de la primera dosis, pero estos síntomas se resolvieron al final del tercer día del tratamiento con naltrexona, cuando ambos pacientes toleraron la tableta de 50 mg como mantenimiento.

CONCLUSIONES: Los líquidos de naltrexona de 1 mg/mL preparados tanto con tabletas como con polvos son estables cuando se almacenan a lo oscuro por 60 días a 4 °C y por 30 días a 25 °C. La fórmula preparada

Appendix I. NIDA Formulation of Naltrexone (10 mg/mL) Oral Liquid

Naltrexone HCl	10 mg
Ascorbic acid USP	5 mg
Sodium saccharin NF	1 mg
Sodium benzoate	1 mg
Sorbitol solution, 70% USP	0.4 mL
Peppermint oil, NR	0.00085 mL
FD&C yellow #5	0.2 mg
Distilled water	≤1 mL

NIDA = National Institute for Drug Abuse.

con las tabletas provee una dosificación flexible para los pacientes que experimentan una deshabituación rápida de la metadona.

LUZ LABRADA-RAVELO

RÉSUMÉ

OBJECTIF: Evaluer la stabilité de la formulation orale liquide de la naltrexone préparée à partir de comprimés et de poudre, et évaluer son efficacité à induire un syndrome de privation de la méthadone.

DEVIS EXPÉRIMENTAL: Une formulation orale de naltrexone 1 mg/mL a été préparée à partir de comprimés et de poudre. On l'a conservée dans l'obscurité à 4, 25, et 70 °C. Des formulations de 5 mg/mL ont été conservées uniquement à 70 °C. La formulation de 1 mg/mL préparée à partir de comprimés a été évaluée pour son efficacité à induire rapidement un syndrome de privation chez deux toxicomanes recevant un traitement d'entretien avec la méthadone. On a utilisé un protocole de doses titrées de la naltrexone.

LIEU D'ÉTUDE: Une faculté de pharmacie et un hôpital universitaire urbain affilié.

MESURES DE L'EFFET: Des échantillons ont été pris six fois. Ils ont été analysés afin de déterminer le degré de décomposition des formulations

au courant de 90 jours. Une liste de contrôle pour les symptômes de privation d'opioïdes a été utilisée avant et une demi-heure après chaque dose de naltrexone afin de mesurer la sévérité de symptômes de privation.

RÉSULTATS: La concentration de la naltrexone dans toutes les formulations conservées à 4 et à 25 °C n'a pas diminuée significativement au courant de 90 jours. Les deux patients ont toléré la formulation orale liquide de la naltrexone 1 mg/mL, mais l'ont trouvée amère et grasse au goût. Les symptômes de privation ont apparu immédiatement suite à la première dose, mais se sont résolus par la fin du troisième jour du traitement avec la naltrexone. À ce point, les deux patients étaient capables de tolérer un comprimé de 50 mg de naltrexone comme dose d'entretien.

CONCLUSIONS: Les formulations à voie orale liquide de la naltrexone 1 mg/mL préparées soit de comprimés ou de poudre sont stables dans l'obscurité pour 60 jours à 4 °C et pour 30 jours à 25 °C. La formulation préparée de comprimés permet une posologie flexible chez les patients qui subissent la privation rapide de la méthadone.

MARIA I RUDIS