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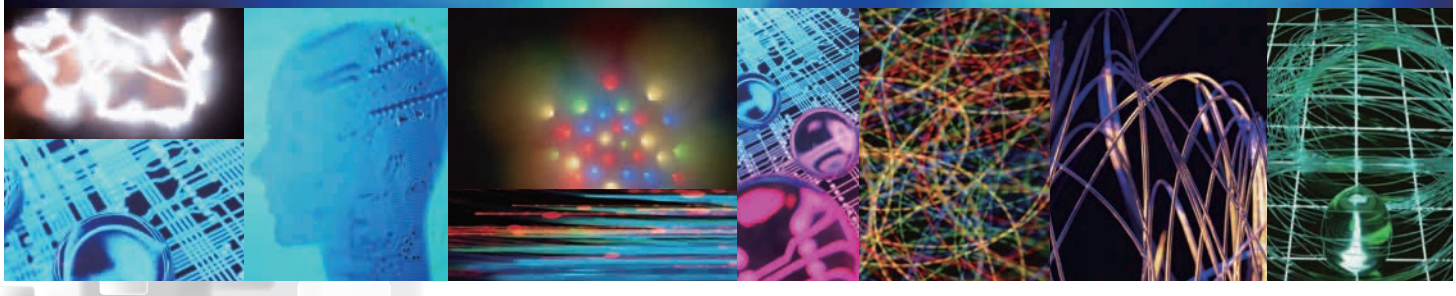

JASPO
一般社団法人 日本臨床腫瘍薬学会

Contents

第17回国際がん薬剤師学会学術大会（上海）に参加して

一般社団法人 日本臨床腫瘍薬学会
理事長　加藤 裕芳

3月の総会およびその後の理事会におきまして理事長に選出されました加藤裕芳でございます。2年間JASPOの発展のために努めてまいります。どうぞよろしくお願いいたします。

2018年4月11日（水）～ 13日（金）国際がん薬剤師学会（ISOPP : International Society of Oncology Pharmacy Practitioners）学術大会が上海のケリーホテル浦東において開催されました。大会テーマ「East Meets West : Past, present, and Future」のもとに世界各国のがん医療に携わる薬剤師たちが集い、すべての国のがん患者に最高の医療を提供するために情報共有や意見交換が行われました。今回私は、ISOPPから招待された遠藤前理事長に代わって大会に参加してきましたので、ここに報告させていただきます。

大学の講義の関係で、私は12日（木）の午後からの参加になりました。会場ではPoster Viewing sessionが行われており、開催国の中国をはじめとして東南アジア、欧米、アフリカ諸国の若手薬剤師たちが発表していました。緊張の中にある流暢な英語のプレゼンテーションや質疑応答、終了した後の彼らの笑顔がとても印象的でした。英語のプレゼンテーションを十分に聞き取ることができない私でもスライドを見ることで、研究の内容はおおむね把握できました。発表は調査を中心とした臨床研究がほとんどで、前向きな調査研究の発表も散見され、研究の質の高さを感じました。一方で治療レジメンを見ると各国の経済状況が伺え、高価な分子標的薬や免疫チェックポイント阻害薬に関しての報告はまだまだ少ない気がしました。日本からはがん研究センター東病院の川澄氏から「がん拠点病院におけるがん専門薬剤師の役割に関するアンケート調査」の報告があり、司会者から日本の専門薬剤師制度に関する質問が出るなど注目される発表でした。

翌日、JASPOと大会長Bo Yu氏とのSpecial Session「Oncology Pharmacy Practice in China and Japan-Past, Present and Future」が行われました。会場はほぼ満席となり、大変光栄に感じる中で、私からは、今回の招待のお礼と、このセッションが今後のISOPPとJASPOの友好関係のスタートになることを期待する旨の挨拶をいたしました。その後JASPOの鈴木理事とBo Yu氏が両国のがん医療に関わる薬剤師の歴史と現状そして将来の役割について紹介しました。Bo Yu氏からは「中国における薬剤師の業務は、調剤・製剤が中心で臨床における薬剤師の業務はこれからの課題となっている。中国における臨床薬剤師の普及のためには、日本や諸外国の専門薬剤師制度を参考にしたい」旨の話しがあり、これからのJASPOの協力に期待しているようなコメントをしておりました。また、司会のAlexander Chan氏からはISOPPとJASPOとの協働事業の可能性についての質問があり、私からは「これから協働できる事が何かをお互いに検討し、それらを踏まえて前向きに進めたい」と回答しこのセッションを終えました。その後のClosing Panelでは「Precision Medicine in Oncology」のテーマでJASPOの野村理事とTodd Knepper氏（MOFFITT Cancer Center）からの講演があり、野村氏が紹介した「日本で行われているゲノム解析によるがん治療の個別化について」の

報告は将来のがん薬物療法の主役になると考えられており、参加者からも大変注目される内容でした。

今回この大会に参加してみて、ISOPPは参加費が高いものの敷居はとても低く、どのメンバーも私たちを大変友好的に受け入れていただき、会場の内外でも誰からも気さくに声をかけられていました。特にEvening Eventの黄浦江ナイトクルージングでは、上海の素晴らしい夜景を満喫するとともに、ISOPPの仲間と過ごした楽しい宴が今も一番の思い出として残っております。次回は2019年10月10日（木）～13日（日）にロンドンで開催されます。遠方ではありますが興味のある方々は是非参加して、行った研究を世界に発信するとともに、同じ志を持つ薬剤師とともに語り合い、友情を深めて下さい。

JASPOとしてもこの機会を大切にし、ISOPPとより太い関係を築き互いの発展に努めてゆきたいと思います。今回のJASPOとISOPPの協働セッションのオーガナイズに尽力していただきました鈴木理事に大変感謝いたします。

最後に、2泊3日の短い滞在を終え帰国の途につく際、郊外にある浦東国際空港と上海市内にある虹橋国際空港を間違えてしまい、たどたどしい英語を駆使しながらの上海市内のバス移動、あわてて乗った飛行機も離陸後に急病人の発生により上海へのリターンとハプニング続きの帰国となりました。機内での急病人発生に際して搭乗員の医療従事者を探す呼びかけに「薬剤師ですが何かできることはありますか」と返事した自分に満足し無事羽田に到着しました。私にとってとても思い出深い旅となりました。

日本臨床腫瘍薬学会雑誌の会誌編集委員会委員長の就任に際して

会誌編集委員会委員長
松尾 宏一

この度、日本臨床腫瘍薬学会雑誌（Journal of Japanese Society of Pharmaceutical Oncology）の会誌編集委員会の委員長に就任いたしました。ここに謹んでご報告申し上げます。

本誌は、日本臨床腫瘍薬学会（JASPO）の機関誌として「日常の臨床疑問や様々な業務への取り組みを研究としてまとめ、発表する場を提供するもの」として、平成26年11月に創刊されました。これまでに3年半が経過し、1年に2回の頻度で発刊され、今回が第8巻となります。

これまで、学会からの情報発信を基本とした項目と論文投稿の項目の2本立てで構成して参りました。情報発信の部分では、その時点での最新の話題を記事として提供し、また論文投稿の項目では、現在までに会員の皆様より24報が投稿され、査読審査により、原著論文3報、短報4報、症例報告2報が掲載され、有意義な知見を広く発表することができました。これも本学会における皆様の活発な研究活動の賜物と存じます。

今回、本委員会は一部の委員を変更いたしました。これを機に、一同で本誌の発展にいっそう努力してまいる所存でございます。何とぞ、今後とも会員の皆様の益々のご支援を賜りますようよろしくお願い申し上げます。

原　著

バンコマイシン塩酸塩点滴静注時の造血器腫瘍と固形腫瘍における薬物動態パラメータの比較

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橋本 浩伸，大塚 知信，寺門 浩之
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Comparison of the pharmacokinetics of vancomycin hydrochloride between hematological malignancies and solid tumors

Summary

Pharmacokinetic parameters of vancomycin hydrochloride (VCM) have been reported to be affected by the presence of malignancy. This study aimed to clarify the differences in the pharmacokinetic parameters of VCM between hematological malignancies and solid tumors, which have not been clarified previously. We retrospectively investigated the pharmacokinetic parameters of VCM between patients with hematological malignancies (n = 256) and solid tumors (n = 197) . Our results indicated that VCM clearance was significantly higher in patients with hematological malignancies than in patients with solid tumors. The volume of distribution and half-life of VCM were significantly lower in patients with hematological malignancies than in patients with solid tumors. In conclusion, the results of this study revealed significant differences in the pharmacokinetic parameters of VCM between patients with hematological malignancies and solid tumors.

Key words

Vancomycin hydrochloride, pharmacokinetic parameter, hematological malignancy, solid tumor

要旨和訳

バンコマイシン塩酸塩（vancomycin hydrochloride:以下、VCM）の薬物動態パラメータの変動要因として悪性腫瘍の罹患が報告されているが、がん種間で VCM 薬物動態パラメータを比較した報告は少なく、検討されたがん種も限られている。そこで本研究では後方視的に悪性腫瘍患者での VCM 薬物動態パラメータについて造血器腫瘍（n = 256）と固形腫瘍（n = 197）で比較し、検討を行った。固形腫瘍と比較し、造血器腫瘍において VCM 全身クリアランスは有意に高かった。分布容積および半減期については固形腫瘍と比較して造血器腫瘍で有意に低かった。これらの結果より、悪性腫瘍罹患だけでなく、がん種によっても VCM の薬物動態パラメータに違いがある可能性が示唆された。

キーワード　バンコマイシン塩酸塩，薬物動態パラメータ，造血器腫瘍，固形腫瘍

〔受付：2018年３月５日　受理：2018年５月７日〕

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緒言

グリコペプチド系抗菌薬であるバンコマイシン塩酸塩（vancomycin hydrochloride：以下、VCM）は、グラム陽性球菌に対して優れた抗菌活性を有し、主にメチシリン耐性黄色ブドウ球菌（Methicillin-resistant *Staphylococcus aureus*：以下、MRSA）治療に用いられる薬剤である。がん領域で VCM は、化学療法に伴う発熱性好中球減少症（febrile neutropenia：以下、FN）治療において MRSA などの薬剤耐性グラム陽性球菌感染症が強く疑われる状況で用いられる場合が多い[1]。VCM の血中濃度は有効性および腎機能障害の発現に関係することが報告されていることから therapeutic drug monitoring を行うことが推奨されている[2]。

近年では、VCM 薬物動態パラメータの変動要因の一つとして悪性腫瘍罹患が報告されている[3-6]。これまでに小児悪性腫瘍患者において非悪性腫瘍患者と比較して VCM の全身クリアランス（以下、CL_{VCM}）が増大し、半減期（以下、$t_{1/2}$）が短縮したとの報告がある[3]。また、非悪性腫瘍患者と比較して造血器腫瘍患者において CL_{VCM} が有意に増大したとの報告もある[4]。寺町らは日本人悪性腫瘍患者において、非悪性腫瘍患者と比較して CL_{VCM}、分布容積（以下、Vd）が有意に増大したと報告している[6]。また、寺町らはこの報告の中で、がん種間における VCM 薬物動態パラメータの違いについて検討しているが、症例数が少なく明らかにはなっていない。

これまでに少数ながら悪性腫瘍患者における VCM 薬物動態パラメータの違いについての検討はなされているが、症例数が少なく、検討されたがん種も限られており、明確にはなっていない。そこで本研究では、悪性腫瘍患者における VCM の薬物動態パラメータについて造血器腫瘍と固形腫瘍で比較し、その違いについて検討した。

方法

1．対象患者

2012 年 11 月～2014 年 11 月までに国立がん研究センター中央病院（以下、当院）で、VCM が静脈投与された症例 453 例を調査対象とした。ただし、血液透析患者、持続的血液ろ過透析患者および持続的腹膜透析患者と小児患者（12歳以下）は除外した。

2．調査項目

対象症例のがん種、年齢、性別、身長、体重、血清クレアチニン値（以下、Scr）、FN の有無、定常状態に達したと考えられる 3 日目以降に採取された点滴開始直前（trough 値）および点滴終了 1 時間後または 2 時間後（peak 値）の VCM 血中濃度について後方視的に調査した。クレアチニンクリアランス（以下、CLCr）はCockcroft-Gaultの式を用いて算出し、Augmented Renal Clearance（ARC）はCLCr > 120 mL/min と定義した[7]。

3．VCM薬物動態パラメータの算出

各症例の VCM 薬物動態パラメータの算出には、投与開始 3 日目以降の trough 値および peak 値の 2 点の VCM 血中濃度を用いた。収集した情報をもとに 1-コンパートメントモデルに従い modified Sawchuk-Zaske 法[8] により、CL_{VCM}、Vd および $t_{1/2}$ を算出した。血清中の VCM 濃度は化学発光免疫測定法により ARCHITECTi 1000SR®（アボットジャパン）を用いて測定した。

4．統計

造血器腫瘍群および固形腫瘍群の 2 群間について統計学的解析を行った。Mean 値の比較にunpaired *t*-test、男女比、ARC 症例数および FN 症例数の比較についてはChi-square test を用いて有意差検定を行った。年齢もしくは身長とVCM の各薬物動態パラメータの相関関係は回帰分析により解析した。統計ソフトは JMP®11（SAS Institute Inc, Cary, NC, USA）を用い、$p<0.05$ であるとき有意と判断した。

5．倫理的配慮

本研究は、国立がん研究センター研究倫理審査委員会の承認を得て実施した（承認番号 2014-251）。個人データは個人情報保護に十分配慮したうえで管理した。

結果

1．患者背景

対象症例の患者背景およびがん種の内訳をそれぞれ表 1 および表 2 に示す。全症例数は 453 例、造血器腫瘍群および固形腫瘍群はそれぞれ 256 および 197 例であった。両群の患者背景の比較において年齢、身長、ARC 症例数、FN 症例数、peak 値および trough 値に関して有意な差が認められた。また、FN 症例のうち ARCを発現していた症例は造血腫瘍群で 73 例（70.9%）、固形腫瘍群で 0 例（0.0%）であった。男女比、体重、Scr および VCM 投与開始から採血までの日数については有意な差は認められなかった。がん種の内訳については、造血器腫瘍群では白血病および悪性リンパ腫が、固形腫瘍群では胃がんおよび食道がんがそれぞれ多かった。

表１　患者背景

	全症	造血器腫瘍群	固形腫瘍群	p 値 *
症例数	453	256	197	
性別（男性／女性）	276/177	160/96	116/81	0.439 †
年齢（歳）	57.2 ± 15.5	51.6 ± 15.2	64.5 ± 12.5	<0.001 ‡
身長（cm）	163.2 ± 9.0	164.8 ± 8.3	161.0 ± 9.5	<0.001 ‡
体重（kg）	57.0 ± 11.3	57.9 ± 10.9	55.9 ± 11.8	0.064 ‡
Scr（mg/dL）	0.7 ± 0.3	0.6 ± 0.2	0.7 ± 0.3	0.387 ‡
CLCr（mL/min）	108.7 ± 54.8	118.2 ± 51.4	96.5 ± 56.7	<0.001 ‡
ARC 症例数（%）	141（25.2）	103（40.2）	38（19.1）	<0.001 †
FN 症例数（%）	153（33.8）	145（56.6）	8（4.1）	<0.001 †
FN 症例中 ARC 発現症例数（%）	73（16.1）	73（70.9）	0（0.0）	
peak 値（μg/mL）	29.8 ± 8.6	30.2 ± 7.5	29.1 ± 9.8	0.024 ‡
trough 値（μg/mL）	11.2 ± 5.5	10.6 ± 5.0	12.0 ± 6.2	0.015 ‡
VCM 投与開始から採血までの日数（日）	3.9 ± 1.2	3.9 ± 1.2	4.0 ± 1.2	0.303 ‡

mean±S.D.
* 造血器腫瘍群と固形腫瘍群での検定
† Chi-square test, ‡ unpaired *t*- test

表２　対象症例のがん種の内訳

造血器腫瘍（n = 256）	白血病	119
	悪性リンパ腫	95
	骨髄異型性症候群	25
	多発性骨髄腫	8
	その他	9
固形腫瘍（n =197）	胃がん	30
	食道がん	28
	胆管がん	23
	肺がん	22
	大腸がん	22
	骨軟部腫瘍	15
	乳がん	11
	膵がん	9
	皮膚がん	9
	脳腫瘍	8
	頭頸部がん	6
	婦人科がん	5
	膀胱がん	5
	肝がん	2
	原発不明がん	2

２．薬物動態パラメータの比較

全症例、造血器腫瘍群および固形腫瘍群の VCM の薬物動態パラメータを表３に示す。患者背景において２群間で有意な差が認められた年齢、身長と全症例での VCM の各薬物動態パラメータの相関関係について解析した結果、年齢と$t_{1/2}$（$p < 0.001$、R^2 値 0.280）および年齢と Vd（$p < 0.001$、R^2 値 0.253）でそれぞれ低い正の相関関係はみられた。その他については R^2 値は 0.1 未満であり、明らかな相関関係は認められなかった。VCM 薬物動態パラメータについては、固形腫瘍群と比較して造血器腫瘍群では CL_{VCM} は有意に高値であり（$p = 0.049$）、Vd および $t_{1/2}$ については有意に低値であった（$p < 0.001$）。ARC 発現症例を除外した造血器腫瘍群と固形腫瘍群の VCM 薬物動態パラメータを比較した結果、固形腫瘍群と比較して造血器腫瘍群では $t_{1/2}$（$p = 0.041$）および Vd（$p < 0.001$）は有意に低値であったが、CL_{VCM} については有意な差は認められなかった（$p = 0.721$）。

表３　全症例における薬物動態パラメータの比較

薬物動態パラメータ	全症例（n = 453）	造血器腫瘍（n = 256）	固形腫瘍（n = 197）	p 値 *
CL_{VCM}（L/hr/kg）	0.074 ± 0.027	0.076 ± 0.028	0.071 ± 0.025	0.049 †
Vd（L/kg）	0.77 ± 0.23	0.72 ± 0.21	0.83 ± 0.24	<0.001 †
$t_{1/2}$（hr）	8.11 ± 3.56	7.45 ± 3.47	8.96 ± 3.52	<0.001 †

mean±S.D.
* 造血器腫瘍群と固形腫瘍群での検定
† unpaired *t*-test

表４　ARC 発現例を除いた薬物動態パラメータの比較

薬物動態パラメータ	全症例（n = 312）	造血器腫瘍（n = 153）	固形腫瘍（n = 159）	p 値 *
CL_{VCM}（L/hr/kg）	0.067 ± 0.023	0.067 ± 0.025	0.067 ± 0.022	0.721 †
Vd（L/kg）	0.80 ± 0.23	0.76 ± 0.22	0.84 ± 0.24	<0.001 †
$t_{1/2}$（hr）	9.11 ± 3.59	8.79 ± 0.29	9.43 ± 0.28	0.041 †

mean±S.D.
* 造血器腫瘍群と固形腫瘍群での検定
† unpaired *t*-test

考察

VCM を投与した悪性腫瘍患者における薬物動態パラメータを比較した報告は、ホジキンリンパ腫、脳腫瘍、肺がん、乳がん、膀胱がんおよび肝がんを対象とした寺町らの報告が存在する[6]。しかしながら、寺町らの報告は 25 例と少数例であり、詳細な検討については行われていない。そこで本研究では、VCM 投与患者を造血器腫瘍群と固形腫瘍群の 2 群に分け、VCM 薬物動態パラメータを比較し、その違いについて検討した。

本研究の対象症例全体の VCM 薬物動態パラメータは、CL_{VCM} 0.074（L/hr/kg）、Vd 0.77（L/kg）、$t_{1/2}$ 8.11（hr）であった。過去に Sadoh ら、望月らおよび寺町らが報告した日本人悪性腫瘍患者の薬物動態パラメータはそれぞれ CL_{VCM} 0.051～0.077（L/hr/kg）、Vd 0.90～1.29（L/kg）、$t_{1/2}$ 5.66～23.6（hr）であった[5, 6, 8]。本研究の対象症例と比較すると、Vd については過去の報告よりも低値ではあったが、CL_{VCM} および $t_{1/2}$ については過去の報告と一致していた。本研究の対象症例全体の Vd が過去の報告と比較して低値であった理由については、modified Sawchuk-Zaske 法と Bayesian 法との解析の違いによるものや、対象症例に含まれるがん種による違いによる影響が考えられるが、この点については明らかでない。

造血器腫瘍群と固形腫瘍群における VCM 薬物動態パラメータについては、$t_{1/2}$ および Vd は 固形腫瘍群と比較して造血器腫瘍群で有意に低値であった。これまでに $t_{1/2}$ に関する造血器腫瘍と固形腫瘍を比較した報告はないが、Vd に関しては乳がんが他の悪性腫瘍と比較して高い傾向にあったと報告している[6]。これは本結果とは異なってはいるが、我々の対象症例が乳がんだけでなく 15 種類の固形腫瘍全体の Vd であることが影響している可能性があると考える。また、今回 Vd および $t_{1/2}$ に関しては、2 群間で患者背景に有意な差が認められていた年齢により相関関係が認められた。Ducharme らは、Vd は、< 40歳で 0.58（L/kg）、40－60 歳で 0.65（L/kg）、> 60 歳で 0.75（L/kg）と、若年者ほど Vd は低値であるという結果と一致していた[9]。しかしながら、本研究においては、R^2 値が 0.2－0.3 の範囲内であり、本解析における Vd および $t_{1/2}$ への年齢の影響は極めて低いと考える。

造血器腫瘍群と固形腫瘍群における CL_{VCM} については、固形腫瘍群と比較して造血器腫瘍群で有意に高値であった。寺町らの報告によると、がん種別での検討において、ホジキンリンパ腫が固形腫瘍と比較して CL_{VCM} が高い傾向にあったことを報告している[6]。寺町らの報告は造血器腫瘍 5 例、固形腫瘍 20例と少数例での検討であるが、少なくとも本結果の CL_{VCM} が固形腫瘍群と比較し造血器腫瘍群で高値であることと一致していた。また、VCM 投与を行なっている悪性腫瘍患者における CL_{VCM} への影響を考える上で FN および ARC も重要である。FN 発症率については、がん治療において固形腫瘍と比較すると、造血器腫瘍に対する治療での発症率が高く[10]、これまでに造血器腫瘍の治療に関連する FN 発症下において炎症反応により VCM の腎クリアランスが増大する現象である ARC が報告されている[11, 12]。また、Shimamoto らは、ARC 発現下で Scr からCockcroft-Gault 式に基づいて算出した CLCr が CL_{VCM} と良好な相関関係があることを報告している[13]。本研究では、固形腫瘍群と比較して造血器腫瘍群において有意に多くの FN および ARC 症例を含んでおり、FN 発症例の 70 % 以上が ARC を発現していた。ARC 非発現症例における両群の比較において CL_{VCM} には有意な差は認められなかった。このことから、造血器腫瘍群で CL_{VCM} が高値であった一因として FN 発症に伴う ARC が影響している可能性があると考えられる。また、ARC 非発現症例における比較において$t_{1/2}$ および Vd に関しては有意な差が認められており、これら薬物動態パラメータに関しては ARC 以外の要因の関与も示唆された。固形腫瘍および造血器腫瘍症例のVCM 薬物動態パラメータに違いが生じる機序に関しては不明な点は多く、今後の検討課題であると考えるが、固形腫瘍症例と造血器腫瘍症例では VCM 薬物動態パラメータ による違いから、同一血中濃度を維持するために必要な VCM 投与量が異なる可能性が考えられるため注意が必要である。

がん治療において感染治療は予後に影響を与えうる。特に VCM は、必要時早急に投与を開始し、適切な血中濃度に維持することが重要である。これまでの報告により、悪性腫瘍患者と非悪性腫瘍患者において VCM 薬物動態パラメータが異なると報告されており、同じ血中濃度を維持するために、必要な投与量が異なることが示唆されている[4, 6]。今回の我々の研究により、非悪性腫瘍患者と悪性腫瘍患者だけでなく、さらに造血器腫瘍と固形腫瘍において VCM 薬物動態パラメータが異なっていることが示唆された。このことから、悪性腫瘍患者においてがん種によりさらに VCM 薬物動態パラメータが異なり、これにより VCM の用法、用量が影響を受ける可能性があることを考慮する必要があると考える。2016 年 6 月に刊行された抗菌薬 TDM ガイドライン[14] においては悪性腫瘍患者に対する VCM 投与設計についての記載は十分とは言えない。本研究の結果より、複数回の採血は侵襲性を伴うためルーチンでは必要ないかもしれないが、悪性腫瘍患者へ VCM 投与を行う際は、ARC を発現し

ている造血器腫瘍患者等では症例を選び trough 値と peak 値の２点を測定し、患者の VCM 薬物動態パラメータを算出し投与設計を行なうことを検討してもよいと考える。

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原　著

Formulation of three-compound xyloglucan-based gel for malodorous fungating tumors

Tatsunori Toraishi[1, 2], Masanaho Sasatsu[1], Kaoru Hirose[2], Takeshi Itabashi[1], and Hiroshi Wachi[1]

Summary

This study investigated a novel three-compound gel （XSP gel） formulation with deodorizing effects on malodorous fungating tumors; the gel contains xyloglucan, sucrose, and polyethylene glycol （PEG） as a base. The XSP gel was prepared using different molecular weights （MW） and additive amounts of PEG to investigate changes in gelation time and physical properties such as gel strength. Furthermore, metronidazole （MTZ） was added to the XSP gel to prepare an MTZ-XSP gel and its gelation time, physical properties, and drug release were investigated. PEG shortened the gelation time and strength of the XSP gel, which changed with alterations in the PEG MW and additive amount. This suggests that it is possible to prepare a gel with controlled gelation time and strength by changing the MW and additive amount of PEG. The change in the gelation time and the physical properties of the XSP gel due to the addition of MTZ did not hinder the usefulness of the XSP gel. The drug release of all the MTZ-XSP gels was inhibited depending on the additive amount of PEG. Moreover, MTZ was incorporated into the gel, which inhibited its release compared with that from Rozex®. The above findings suggest that the MTZ-XSP gel has a controlled gelation time and strength and would be a novel formulation with deodorization effects on malodorous fungating tumors.

Key words

xyloglucan, hydrogel, metronidazole, malodorous fungating tumors

要旨和訳

キシログルカン、スクロース、ポリエチレングリコール（PEG）を基剤とした3成分系ゲル（XSPゲル）を用いてがん性皮膚潰瘍臭改善作用を持つ新規剤形の検討を行った。XSPゲルはPEGの分子量、添加量を変えゲルを調製し、ゲル化時間やゲル強度など物性の変化について検討した。さらに、XSPゲルにメトロニダゾール（MTZ）を導入したゲル（MTZ-XSPゲル）を調製し、ゲル化時間、ゲル物性および薬物放出について検討した。

XSPゲルは、PEGの分子量や添加量の変化に伴い、ゲル化時間は短縮し、ゲル強度は変化した。従って、PEGの分子量、添加量を変化させることによりゲル化時間とゲル強度を制御したゲルの調製が可能であると考えられた。MTZの添加によるゲル化時間やゲル物性への変化は、XSPゲルの有用性を妨げないものであった。MTZ-XSPゲルからのMTZの薬物放出は、PEGの添加量依存的に抑えられていた。また、MTZはゲルの中に保持されているため、ロゼックス®に比べ薬物放出が低いことが示された。

以上より、MTZ-XSPゲルはゲル化時間と強度を制御でき、がん性皮膚潰瘍臭改善作用を持つ新規剤形になり得る可能性が示された。

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Introduction

In patients with tumor cells close to the surface of the body such as breast cancer, the tumor may be exposed at the body surface. The exposed tumor cells may self-destruct forming cancerous skin ulcers that release an offensive or unpleasant odor and are called malodorous fungating tumors. In previous epidemiology studies, malodorous fungating tumors were reported in 5–10% of patients with breast cancer[1, 2]. Patients who develop this condition experience notably increased physical pain, and their quality of life (QOL) decreases markedly. The malodorous fungating tumors are caused by the polyamine odorants putrescine and cadaverine produced by tissue decay and volatile short-chain fatty acids such as butyric and valeric acids, which are metabolites of microorganisms such as *Bacteroides fragilis, Prevotella, Fusobacterium nucleatum, and Clostridium perfringens* that grow in areas with deep skin ulcers. Metronidazole (MTZ), a nitroimidazole antibiotic that exhibits bacteriostatic and bactericidal effects by inhibiting DNA synthesis of anaerobic bacteria, has shown efficacy in this condition[3, 4]. The guidelines on symptom relief in terminal illness by the World Health Organization and "Alleviation of cancer symptoms" by the American Society of Clinical Oncology recommend local treatment with a topical agent to avoid the adverse effects of MTZ.

In foreign countries, topical medications containing MTZ are used to treat vaginal trichomoniasis, acne rosacea, and periodontal diseases[5, 6]. In Japan, there was no over-the-counter MTZ preparation and, therefore, hospital preparations were used when it was indicated for malodorous fungating tumors[7-10]. The paste form of a gel containing MTZ (Rozex®: ROZ) approved for the first time in the United Kingdom and globally in 1994 for malodorous fungating tumors was also approved in Japan in 2014 and is currently used clinically.

ROZ is a topical gel in a paste form with good spreadability. When used to treat the surface wound, an appropriate amount for the size of the wound surface must be applied. However, it is difficult to ensure that the ROZ is evenly spread on the wound surface. Moreover, MTZ was shown to be ineffective as a covering material in a clinical study[8]. Thus, when it is applied to a wound surface, a covering material such as gauze needs to be applied. Considerable fluid leakage from the wound surface cannot be contained by gauze and ROZ alone, and contamination of the wound surface and surroundings may occur with bacteria growth. In contrast, when there is little leakage of fluid, the moisture of the gel evaporates, causing the gauze to adhere to the wound surface making it difficult to remove and the skin surface peels off. Therefore, a novel preparation that is effective as a cover material for malodorous fungating tumors and has water absorbing properties, supplies moisture to the wound surface, and can control drug release would likely curb the decline in the QOL of patients.

Cancerous tissue that is exposed on the body surface differs from normal tissue in that the wound surface becomes bare and the skin loses its barrier capacity. Thus, rather than a soft gel, the dressing form of preparation with efficient covering and protective features would be more appropriate. Moreover, the condition of the wound surface differs according to the patient, and since the skin has lost its barrier function, the sensation invoked by the preparation likely differs between patients. Therefore, hardness and flexibility need to be controlled when formulating tailor-made preparations. Moreover, the shape of the malignant wound surface is complicated by the patient. To prepare tailor-made formulations suitable for the complicated wound surfaces that differ according to patients, certain factors need to be considered. For instance, the control of forming time is also an important property of the preparation.

Contrary to semisolid preparations such as ointments and creams, hydrogels have water-retaining capacity and cause less irritation to the skin. Gels form a reticular structure with molecular chains of the basic skeleton, and solvent molecules are held there. The cross-linking structure between molecules that form gels allows them to display various physical properties. Therefore, gel strength and gelation time differ according to the additives. The choice of additive controls the physical properties of gels. If such a preparation is made available clinically, it could be indicated for various wound surfaces and likely improve the QOL of patients.

Xyloglucan is a water-soluble polysaccharide

derived from the tamarind seed. It has a cellulose skeleton with glucose as the main chain while xylose and galactose are the side chains[11, 12]. It is commonly used not only as a food additive but also to promote wound healing and is currently under investigation as a deglutition aid jelly because it controls drug absorption from the oral and nasal mucosa in patients with swallowing disorders[13-15]. Xyloglucan does not form a gel independently in aqueous solution. However, in the presence of a sugar at a concentration of 40–50% or alcohol, xyloglucan forms a gel[16, 17]. The gelation mechanism involves the cross-linking of hydroxyl group of sugar and water molecules with the xyloglucan molecules. This gel has a three-dimensional, resilient structure and is safe. Furthermore, the use of xyloglucan-sucrose gels as wound dressings has been reported, and they are easy to fit on the skin and highly safe[18]. However, with only sucrose, the amount added is large. Moreover, the process of gelation is rapid and the gelation time is difficult to control. Therefore, the aim of this study was to introduce a hydroxyl group-containing substance as a new compound into the xyloglucan-sucrose gel to create a three-compound gel. This new preparation likely has controllable gelation time and physical properties such as gel strength (Fig. 1).

Polyethylene glycol (PEG) is an amphiphilic substance with hydroxyl groups and fully water miscible. This characteristic is likely attributable to the hydrogen bonding between the ether oxygen of the PEG chain and water molecules[19]. Moreover, PEG has numerous molecular weight (MW) forms. Gelation would likely be affected when a straight chain polymer form of PEG with various MWs is used. Therefore, PEG was selected as a third compound in the xyloglucan-sucrose gel. If gelation time and physical properties of the gel could be controlled in a three-compound gel consisting of xyloglucan, sucrose, and PEG (XSP), it could become a clinically useful novel preparation.

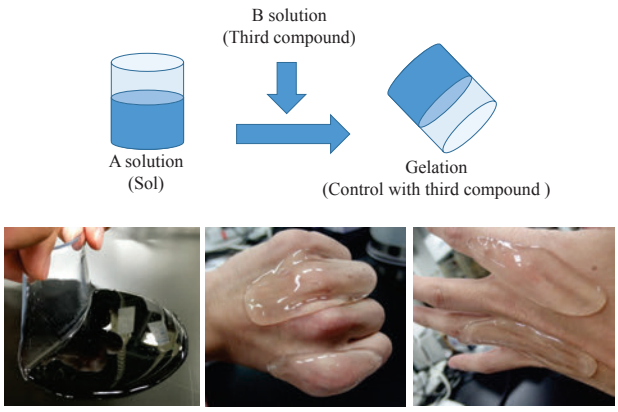

Figure1. Scheme of xyloglucan sucrose gel third material and digital photograph of time dependent xyloglucan sucrose polyethylene glycol gel (XSP gel)

As shown in Fig. 1, the XSP gel is highly adherent to the skin, resilient, and versatile, which make it suitable for use on various wound surfaces. Therefore, application of the XSP gel to wound surfaces associated with malodorous fungating tumors would likely control the malodor, thereby improving the QOL of the patient. In this study, the characteristics of the XSP gel were investigated by changing the MW and the additive amount of PEG. Furthermore, MTZ was introduced into the gel (MTZ-XSP) and the same endpoints were investigated. The investigated MTZ-XSP gel contained PEG MW 400, which was the medium MW PEG studied and used to obtain all the data on the additive amount of PEG. The concentration of MTZ was set at 0.75%, based on the reports on ROZ gel and studies by Finlay et al.[20].

Experimental

Materials

Xyloglucan used in this study was supplied by DSP Food and Chemical Co., Ltd. (Osaka, Japan). Sucrose and PEG were provided by Wako Pure Chemical Industries, Ltd. (Osaka, Japan), and MTZ was from Tokyo Chemical Industry Co., Ltd. (Tokyo, Japan). All other chemicals were obtained commercially at the purest grade available.

Preparation of gels

The xyloglucan solution was prepared using the prescription presented in Table 1. The MTZ sample was added to the XSP gel to achieve a concentration of 0.75%. This mixture was completely dissolved to obtain solution A. Then,

Table 1. Preparation of A solution and B solution

	Material	8%	10%	12%	14%
		Concentration of materials % (w/w)			
A solution	Xyloglucan	2	2	2	2
	Sucrose	20	20	20	20
	Purified water	58	58	58	58
B solution	PEG	8	10	12	14
	Purified water	12	10	8	6

various amounts of PEG were prepared in purified water and mixed to the preparation to obtain solution B. A stirrer equipped with a 50 mm diameter propeller and brushless direct current motor (BL 1200 ; Shinto Scientific Co., Ltd., Tokyo, Japan) was used to stir solution A at 1200 rpm while adding solution B over a 2 min period, and then the solution was stirred for a further 1 min to prepare the gel.

Physical appearance of gels

The gel was prepared using the prescription in Table 1, and then the prepared solution was injected into a screw-top test tube and left to rest for 24 h at 25 ° C as the test sample. The gel was imaged to examine its physical appearance.

Gelation time of gels

Gelation time was examined using the tilting method of Hanawa [21]. The test sample solution was prepared in a 100-mL beaker and left for a predetermined time, and the time when the gel sample could be tilted without flowing was considered the gelation time.

Transmission Temperature of gels

The transmission temperature was determined using the gel tilting and ball drop method, which was previously reported by Kawamura et al. and Hanawa[21, 22]. A 10 mL volume of the prepared solution was injected into a test tube (2.5 mm in diameter and 65 mm long) with a stainless ball (1.2 mm in diameter, 8.5 g in weight) at the bottom and left to stand for 24 h at 25 ° C as the test sample. The sample was inverted in a water bath, the temperature of the water bath was increased at the rate of 2 ℃ /min from 25 ℃ and the temperature at which the stainless ball in the gel dropped was the transmission temperature.

Mechanical properties of gels

The mechanical properties were measured using a rheometer (RTC-2005D･D, RHEOTEC, Co., Ltd., Tokyo, Japan) . At 24 h after preparing the gel, a sample (50 mm in diameter and 35 mm long) was set in a glass sample holder with the same internal diameter of the sample and loaded onto the device, and a 10-mm diameter plunger was lowered at a constant speed (20 mm/min) and measurements were recorded over time until the strain was 0.9. The stress was calculated using equation (1) from the applied load data obtained, and maximum stress was subsequently calculated. The strain was calculated using equation (2) below, and then the modulus of elasticity (Young's modulus) was calculated using equation (3) .

$$\text{Maximum stress (kPa)} = \text{applied load (N)} / \text{cross sectional area of the plunger (mm}^2\text{)} \times 1000 \quad (1)$$

$$\text{Strain} = \text{length to reach maximum stress (mm)} / \text{base length (mm)} \quad (2)$$

$$\text{Modulus of elasticity (MPa)} = \text{maximum stress (kPa)} / \text{strain} \times 100 \quad (3)$$

Water absorption capacity of gels

The water absorption capacity was evaluated using a water absorption apparatus of Nakamura et al. [23]. This apparatus has a glass tube, which is filled with purified water and connected to a glass filter (15 mm in diameter). Briefly, the gel sample weighing 1.5 g with a 15 mm diameter, was placed on the glass filter, which was placed on membrane filter (0.8μm pore size, ADVANTEC, Tokyo, Japan), and the amount of water absorbed after 2 h was measured.

Drug release of MTZ-XSP gels

The drug release was investigated using Franz diffusion cells as previously reported by Watanabe et al[24]. The Franz diffusion cell with a 20-mm diameter orifice and receiver chamber (45.0 mL volume) was used. The drug release behavior in phosphate buffer (pH 6.8) was measured. A gel sample (6.0 g) , which matched the morphology of the donor compartment of the Franz cell, was prepared and loaded into the donor compartment. Then, the receiver compartment was absorbed over time, and the absorbance was measured using a UV spectrophotometer (UV-1800, Shimadzu Corp., Kyoto, Japan) . The concentration of MTZ was calculated based on the absorbance. For comparison, the same process was performed using ROZ, and the measurement wavelength of the UV absorption was 320 nm.

Result and Discussion

Physical appearance of gels

The measurements of the physical appearance of the gels are shown in Fig. 2. The results showed that the gel could be formed by adding solution B (PEG solution) to solution A

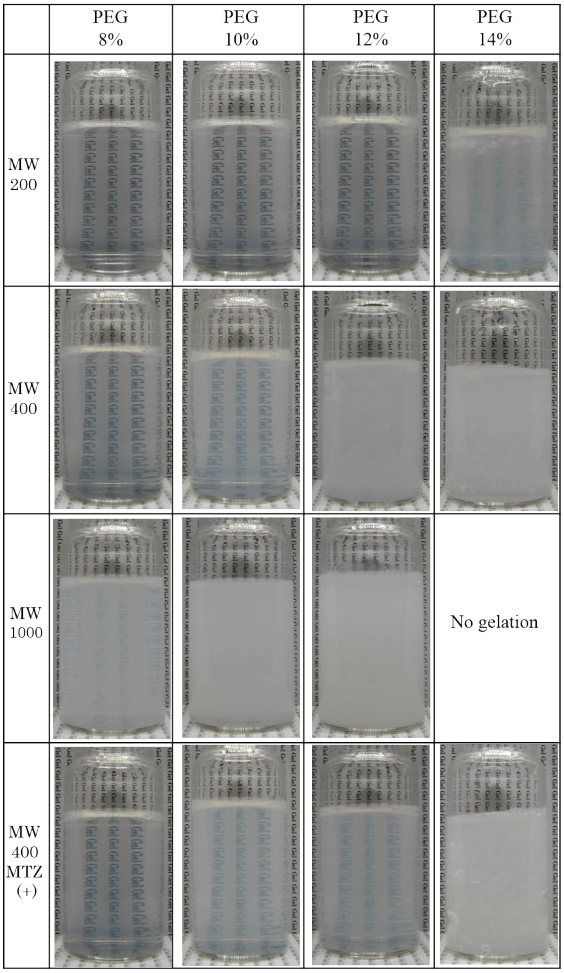

Figure 2. Physical appearance of XSP gel and MTZ-XSP gel

(xyloglucan and sucrose) . However, the PEG MW 1000 14% produced gelation in particle form. Contrary to other gels, a single structured gel was not formed, and the evaluation revealed "no gelation." As shown in Fig. 2, the gel becomes turbid when the MW of the PEG is increased. Furthermore, increasing the amount of additive, increased the turbidity of the gel. Increased turbidity of the gel indicates an increase in the cross-linking domain, which is a region of high cross-linking density[25] . Several studies have reported that an increase in the cross-linking domain scatters the reflected light, which makes the gel turbid[26-28] . Although the gel was turbid, it was the uniform and the turbid phase did not separate, showing that the formation was structurally sound, except for PEG MW 1000 14%. Thus, an increase or decrease in the cross-linking domain by the addition of PEG could significantly affect the physical properties such as the strength and stability of the XSP gel.

The MTZ-XSP gel exhibited some yellow color changes; however, similar to the XSP gel, increased turbidity was observed with an increased amount of additive. PEG 12% decreased the gel turbidity with the introduction of MTZ. This suggests that the formation of the cross-linking domain in the gel was possibly inhibited by MTZ, which likely affected the physical properties of the gel.

Gelation time of gels

Table 2 shows the results of the measurement of gelation time, which decreased depending on the PEG MW and additive amount. Taken together with the results of the physical appearance, these findings suggest that the reaction of cross-linking was enhanced by an increase in PEG MW and amount of additive, which shortened the gelation time. The range of the PEG MW and amount of additive used in this study adequately controlled the gelation time.

In the MTZ-XSP gel, PEG 8 and 14% caused no difference in gelation time compared to that of the XSP gel. However, PEG 10 and 12% prolonged the gelation time of the MTZ-XSP gel. MTZ has two sites in its structure that can form hydrogen bonds. Therefore, it was likely involved in the cross-linking domain of the gel. Moreover, together with the results of the physical appearance, this observation indicates that the introduction of MTZ in the gel formulated with PEG 12% increased the gel transparency compared to that of the XSP gel. This was due to the MTZ-induced inhibition of the cross-linking in the gel. This result showed that the substances with sites that can form hydrogen bonds possibly act by either enhancing or inhibiting forming of the gel cross-linking domain.

Table 2. Gelation time of XSP gel and MTZ-XSP gel (min)

	PEG 8%	PEG 10%	PEG 12%	PEG 14%
MW 200	480	120	30	5
MW 400	240	20	5	3
MW 1000	240	15	5	No gelation
MW 400 MTZ(+)	240	40	10	3

Transmission temperature of gels

Table 3 shows the results of the measurement of transmission temperature, which was evaluated as an index of the stability of the gel structure. The transmission temperatures of all the gels were higher than the human body surface temperature. Therefore, the XSP gel did not melt

Table 3. Transmission temperature of XSP gel and MTZ-XSP gel (℃)

	PEG 8%	PEG 10%	PEG 12%	PEG 14%
MW 200	51.9 ± 0.6	57.1 ± 0.2	60.3 ± 0.3	62.9 ± 0.1
MW 400	54.5 ± 0.3	58.8 ± 0.1	62.0 ± 0.0	63.0 ± 0.1
MW 1000	56.7 ± 0.1	60.0 ± 0.1	59.9 ± 0.1	No gelation
MW 400 MTZ(+)	47.8 ± 0.8	57.7 ± 0.6	59.1 ± 0.1	67.1 ± 0.4

(mean ± SD, n = 3)

on the wound surfaces because of the body temperature. PEG 8 and 10% increased the transmission temperature in an MW-dependent manner, whereas PEG 12 and 14% caused no MW-related difference in the transmission temperature. Moreover, MW 200 and 400 increased the transmission temperature in a manner that was dependent on the amount of additive, whereas the MW 1000, PEG 10 and 12% showed no difference in transmission temperature. This was likely due to the intensified formation of the cross-linking domain because of the increase in PEG MW and amount of additive, which stabilized the gel.

Similar to the XSP gel, the transmission temperature of the MTZ-XSP gel increased in a manner that was dependent on the amount of PEG additive. Compared to the transmission temperature of the XSP gel, that of the MTZ-XSP with PEG 8 and 12% decreased significantly, but the value increased with PEG 14% (PEG 8%, 12%, 14%, P-value < 0.05) . With PEG 14% XSP gel excessively increased the cross-linking domain, and the formation of a non-uniform gel structure decreased the gel stability. The structure of MTZ has two sites where hydrogen bonding can occur and, thus, it is more intricately involved in the cross-linking points.

Mechanical properties of gels

Fig. 3 and Table 4 show the results of the measurements of maximum stress, strain, and modulus of elasticity. With PEG MW 200, the strain was increased in a manner that was dependent on the amount of additive, and the gel

Table 4. Mechanical properties of XSP gel and MTZ-XSP gel

Stress of XSP gel and MTZ-XSP gel (kPa)

MW 400	XSP gel	MTZ-XSP gel	*P*-value
PEG 8 %	6.86 ± 0.31	7.24 ± 1.15	0.63
PEG 10 %	65.19 ± 15.18	59.89 ± 13.60	0.81
PEG 12 %	223.35 ± 26.38	164.33 ± 13.64	0.07
PEG 14 %	173.45 ± 9.03	150.11 ± 45.30	0.47

(mean ± SD, n = 3, *t*-test, $P < 0.05$)

Strain of XSP gel and MTZ-XSP gel

MW 400	XSP gel	MTZ-XSP gel	*P*-value
PEG 8%	0.48 ± 0.02	0.55 ± 0.03	0.05
PEG 10%	0.65 ± 0.04	0.64 ± 0.05	0.81
PEG 12%	0.60 ± 0.02	0.63 ± 0.04	0.41
PEG 14%	0.43 ± 0.01	0.48 ± 0.03	0.16

(mean ± SD, n = 3, *t*-test, $P < 0.05$)

Elastic modules of XSP gel and MTZ-XSP gel (MPa)

MW 400	XSP gel	MTZ-XSP gel	*P*-value
PEG 8%	0.14 ± 0.01	0.13 ± 0.02	0.51
PEG 10%	0.99 ± 0.20	0.93 ± 0.19	0.71
PEG 12%	3.71 ± 0.42	2.62 ± 0.10	0.04 *
PEG 14%	4.00 ± 0.31	3.12 ± 0.74	0.17

(mean ± SD, n = 3, *t*-test, $P < 0.05$)

strength was increased. With PEG MW 400 and 1000, the maximum strength was observed at 10 and 12%, respectively, whereas the addition of more PEG decreased the strength. The stress decreased to the lower value because of the decreased gel strength caused by the cross-linking domain, which was triggered by the increase in the amount of additive. The strain was decreased based on the amount of additive. The high strain values were due to the low MW and low amount of additive, which softened the gel and likely accounted for the lack of gel rupture in the measurements, which made up for the strain level of 0.9. With PEG MW 200 and 400, the modulus of elasticity increased in a manner that depended on the amount of additive, whereas with PEG MW 1000, it was at the maximum value with PEG 10% and subsequently decreased with higher amounts of PEG. According to Nishinari et al.[17] , xyloglucan gel shows the highest gel strength when the amount of additive sugar is approximately 50%. However, the sugar additive in the XSP gel was 20%, and even at this proportion, the subsequent addition of PEG did not increase the total additive

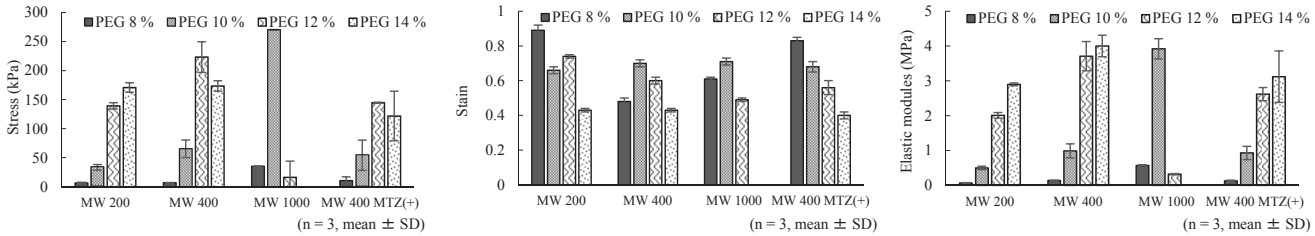

Figure 3. Mechanical properties of XSP gel and MTZ-XSP gel.

Table 5. Mole of PEG of each molecular weight added in 100 g of the gel.(mol)

MW	8%	10%	12%	14%
200	0.040	0.050	0.060	0.070
400	0.020	0.025	0.030	0.035
1000	0.008	0.010	0.012	0.014

to 50%. Furthermore, the gel strength reached its peak because of the effect of the ether oxygen present in PEG. The forming of cross-linking domain due to the ether oxygen had a major effect on the physical properties of the gel. When there were more spots in the gel with the formation of the cross-linking domain, the gel structure became uneven, which decreased gel strength. Table 5 shows the mole of PEG of each MW added in 100 g of the gel. Considering the mole data of added PEG, increasing the MW had a stronger effect than the amount of the additive did. Similar results were obtained in the other experiment. Within the scope of this investigation, modifying the MW and adding a specific amount of PEG to control the forming of the cross-linking domain also likely effectively controlled the gel hardness and flexibility.

The MTZ-XSP gel showed almost similar tendencies to those of the xyloglucan gel. The modulus of elasticity, however, showed a significant difference with PEG 12%. This finding, together with the improved transparency due to the introduction of MTZ, was likely attributable to the MTZ-induced inhibition of the formation of the cross-linking domain. The results show that the hardness and flexibility could be controlled and that it is possible to maintain the dressing form, even if MTZ is added to the XSP gel.

Water absorbability of gels

All the gels maintained their shape and water retention capacity. In addition, the PEG MW1000 12% gel did not absorb water (Fig. 4) . The water absorbability decreased as the gel strength increased. Because the cross-linking domain and formation of the gel are affected, increased gel strength results in a stronger structure, which decreases gel swelling[29-31] .

In the MTZ-XSP gels, the presence of PEG 8% significantly decreased the water absorbability. With PEG 8% MTZ-XSP gel is not strong and has a loose structure and, thus, water could not be retained. Such a significant difference was not observed with incorporation of other amounts of

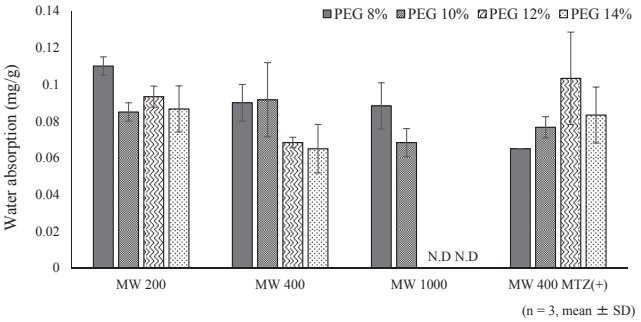

Figure 4. Water absorption of XSP gel and MTZ-XSP gel after 120 min.

PEG. The addition of MTZ to the gels may not inhibit water absorption. The absorption of exudates reportedly inhibits odor production[32] . Therefore, it is necessary to ascertain whether this water absorbency leads to a clinical effect.

Drug release of MTZ-XSP gels

The results of the drug release of the MTZ-XSP gel are shown in Fig. 5. Compared with ROZ, the drug release of all the MTZ-XSP gels was inhibited dependent on the additive amount of the PEG, and the gel retained its shape after the test. On the other hand, ROZ absorbed the receiver solution and became muddy. Table 6 shows the comparison of the correlation coefficient (r^2) of the amount of drug release against the time and the square root of time, to understand the mechanism of drug release. It was more linear to use the square root of time. According to this result, the structure of the gel was not disintegrated by the absorbed receiver solution, and the mechanism of MTZ release was likely by diffusion. However, the percentage release of MTZ calculated from the result was approximately 0.6–13% in 5 h. It is possible that MTZ was retained in the gel structure. Because the gel near the membrane absorbs the receiver solution, the matrix of the gel loosened and MTZ diffused out.

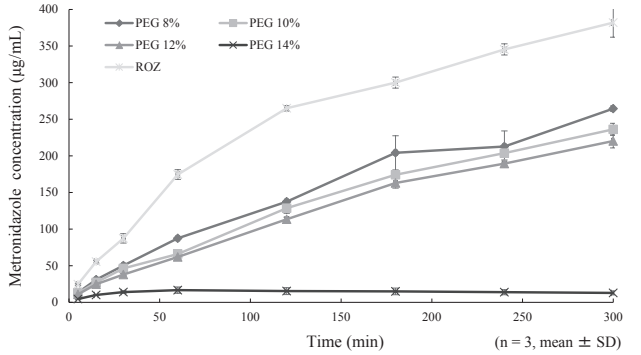

Figure.5 Release profile of MTZ from MTZ-XSP-gel and ROZ.

Table 6. Comparison of the correlation coefficient of the amount of drug release against the time and the square root of time. (r^2)

120 min	PEG 8%	PEG 10%	PEG 12%	PEG 14%	ROZ
Time	0.9725	0.9848	0.9860	0.5069	0.9787
The square root of time	0.9969	0.9834	0.9878	0.8337	0.9933

The observations indicate that MTZ was incorporated in the gel and that its diffusion was inhibited.

Although the minimum inhibitory concentration (MIC) of MTZ differs depending on the bacterium, the range spans approximately 0.5–2 μg/mL[4] . In MTZ-XSP gels, MTZ was retained in amounts that exceeded the MIC from immediately after the start of the test, for all additive amount of PEG used. The barrier function that normal tissues have is absent on wound surfaces such as those of malodorous fungating tumors. The absorption of MTZ in the body has been confirmed[9] . This suggests the possibility of adverse events such as peripheral nerve disorder, central nervous disorder, leukopenia, and neutropenia due to increased blood concentration. Because MTZ-XSP gels release less MTZ than the other formulation, it is possible that the systemic absorption could be inhibited from the malodorous fungating tumor site.

Conclusion

This study describes the formulation of a novel gel with PEG as the third compound in xyloglucan-based gels. The gelation time and physical properties of the XSP gel could be controlled by changing the MW and additive amount of PEG. The incorporation of MTZ only slightly changed the physical properties of the MTZ-XSP gel and involved the crosslinking structure of the gel. However, the gelation time and strength of gels formed using PEG could be controlled, and the release of MTZ could be inhibited compared with that of ROZ. It is necessary to ascertain whether this formulation has clinical effects. Therefore, based on the results of this study, we would like to investigate the effect of this formulation in animal experiments and clinical studies.

In conclusion, the MTZ-XSP gel has the potential of being a tailor-made formulation for a cancerous skin ulcer site with a complex wound surface and a formulation that can be prepared rapidly even at the bedside.

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Conflict of interest

The authors declare that there is no conflict of interest regarding this research.

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